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ORIGINAL ARTICLES.

ANTERIOR PITUITARY TUMOR ASSOCIATED WITH CACHEXIA, HYPOGLYCEMIA, AND DUODENAL ULCER.

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It is common to see symptoms referable to growth and development of the body and changes in the functional capacity of other endocrine organs in association with hypophyseal adenomas; in fact, diagnosis is frequently established on these findings alone even without local pressure phenomena. In the following case, a curious aggregation of symptoms was encountered in association with a tumor of the anterior lobe of the pituitary body, including persistent hypoglycemia, symptoms of cachexia hypophyseopriva, lowered metabolism, and a very active and incapacitating duodenal ulcer. So far as we have been able to ascertain, this particular combination has not previously been described, although each of the presenting symptoms has been noted separately in association with anterior hypophyseal lesions.

Case Report.—A man, a Jew, aged 28, registered at the clinic December 28, 1934, complaining of abdominal pain, vomiting, constipation and anorexia. His history was essentially negative. He had always been in good health and had been able to work steadily until the onset of this present illness a year before. His illness had begun with a sharp, periumbilical pain, occurring at first on 1 or 2 days a week, and later becoming fairly constant except for exacerbations which frequently occurred 3 to 4 hours after meals. He had never had a remission lasting more than a week. As the months progressed, the pain had become more severe and constant, awakening him frequently at night. At first, the distress had been partially relieved by food and soda. Probably because of dietary restrictions, constipation had also

developed and he had used laxatives and enemas freely. No melena or hematemesis had been noted at any time. He had been able to continue work for the first 8 months of his illness but, with the increasing severity of symptoms and subsequent loss of appetite and strength, he had been finally forced to give up his occupation as a laborer. His weight had dropped from 178 pounds to 140 (80.7 to 63.5 kg.), most of this loss having occurred in the 4 months prior to admission to the clinic.

Numerous physicians had been consulted concerning these complaints and the patient had been hospitalized in November, 1934, for complete roentgenologic examination of the gastro-intestinal tract; a dilated colon had been the only positive finding at the time. The patient had noticed no improvement on treatment directed at relief of the colonic stasis, but had become steadily worse and marked anorexia had developed. The smell and sight of food nauseated him; he vomited milk almost immediately after drinking it and the mere mention of food distressed him. There were a few articles of diet which he ate sparingly, but he had lived chiefly on fruit juices for 2 weeks preceding examination at the clinic and during this time vomited once or twice daily.

On examination at the clinic the patient appeared dull and lethargic; he was uncoöperative and unwilling to talk freely. He was 5 feet 9 inches in height (172.5 cm.) and weighed 140 pounds (63.5 kg.). There was evidence of recent loss of weight and the muscular tone was poor. The systolic blood pressure was 110, the diastolic 70. The pulse rate was 90 and the temperature 98.4° F. The general habitus was eunuchoid; his face was smooth and covered by a very fine hair. He shaved once a week. The skin was very dry and body hair was scanty and of the feminine type of distribution. The pupils reacted normally to light and accommodation; the ocular fundi appeared to be normal and the visual fields were negative. The lips were dry, cracked and of a thickened type; the tongue heavily coated; the tonsils were of medium size and cryptic, and there was a pungent, acidotic odor to the breath. The thyroid gland appeared to be normal in size. Examination of the thorax revealed prominent breasts; lungs and heart, normal. The abdomen was slightly distended, soft, and its walls had an unusually thick and doughy consistency. No masses could be palpated, but slight generalized tenderness was noted, more marked in the right upper quadrant. The genitalia were markedly underdeveloped and the prostate gland was smaller than normal. Inflamed hemorrhoids protruded. The deep and superficial reflexes were normal.

The patient was hospitalized on December 28, 1934, and laboratory examinations were carried out as his condition permitted. The value for hemoglobin was 12.15 gm. per 100 cc. of blood; erythrocytes numbered 4,820,000 and leukocytes 8600 per c.mm. A differential count was essentially normal. Serologic tests for syphilis were negative. The urine had specific gravity of 1.025; it was acid and contained albumin graded 2, no sugar, hyaline casts (graded 2) and an occasional pus cell per microscopic field. Subsequent urinalyses were negative.

Venous blood (1 hour after the noon meal on day of admission) contained: urea 20 mg., sugar 43 mg. and chlorides 487 mg. per 100 cc.; the carbon dioxide combining power was 80.5 volumes %. Intravenous infusion of 1 liter of 10% glucose and 1% saline solution was given immediately on receiving these reports and this procedure was repeated daily for 8 days thereafter. The fasting value for blood sugar on the following morning was found to be 60 mg. %; another fasting value was obtained Jan. 2 and was reported as 44 mg. Blood chlorides were 611 mg. %, and carbon dioxide combining power of the plasma was 67.3 volumes % on this date.

The patient was carefully watched and closely questioned regarding symptoms of hypoglycemia, but no evidence of any untoward reaction or

sensation could be elicited. He neither showed nor could recall any symptoms that are commonly noted in spontaneous hypoglycemia or with insulin reactions. Fasting and delay in getting his meals, even when he was working, had never caused him to become weak; he had never noted any excessive sweating, diplopia, attacks of weakness, convulsions, or related conditions. Frequent estimations of blood sugar and chlorides were made during the patient's 31-day stay in the hospital (Table 1). The highest reading for blood sugar obtained at any time was 78 mg. %, the lowest 30 mg. (Jan. 17). These levels were not affected by a high intake of carbohydrate or by intravenous infusions of glucose. The patient vomited glucose solution given by mouth so that the glucose tolerance could not be satisfactorily determined.

TABLE 1.—DETERMINATIONS OF BLOOD SUGAR, CHLORIDES, AND CARBON DIOXIDE COMBINING POWER.

Date.	Time.	Blood sugar, mg. per 100 cc.	Blood chlorides, mg. per 100 cc.	Carbon dioxide combining power volumes %.		
1934.						
12–28	1.30 P.M.	43 60	487	80.5	1 liter 10% glucose and 1% salt, intravenously	One hour after noon meal.
12–29	8.30 A.M.	..	..	..	1 liter 10% glucose and 1% salt, intravenously, daily from Dec. 29 to Jan. 4	Fasting.
1935.						
1– 2	8.30 A.M.	44	611	67.3		Fasting.
1– 4	Noon	..	..	..	1 cc. ant. pit. extract, intramusc.	
1– 5	8.30 A.M. 10.30 A.M.	40 49	676	60.7	...	Fasting.
1– 8	8.30 A.M.	43	544	..	...	Fasting.
1– 9	10.30 A.M.	38	561	..	...	Fasting.
1–11	4.30 P.M.	45	511	..	Operation; transfusion; 500 cc. 20% glucose intravenously, cortin, 10 cc.	After breakfast.
1–12	8.30 A.M. 9.30 P.M.	65 52	544 479	..	500 cc. 20% glucose; cortin, 10 cc. daily	After breakfast.
1–13	8.30 A.M.	65	553	..	Cortin, 10 cc. daily	After breakfast.
1–14	8.30 A.M.	38	561	..	Cortin, 10 cc. daily	After breakfast.
1–15	8.30 A.M.	33	528	..	...	After breakfast.
1–17	8.30 A,M,	30	536	..	Cortin, 10 cc. daily	After breakfast.
1–18	8.30 A.M.	66	503	..	...	After breakfast.
1–19	8.30 A.M.	60	528	..	...	After breakfast.
1–20	8.30 A.M.	59	528	..	...	After breakfast.
1–23	8.30 A.M.	38	561	..	...	Fasting.
1–25	8.30 A.M.	52	..	..	...	Fasting.

In view of the peculiar and unexplained hypoglycemic state and the eunuchoid habitus, the possibility of some pituitary disturbance was at once suspected. A Roentgenogram of the head revealed enlargement of the sella turcica, grade 4, with thinning of the posterior clinoid processes (Fig. 1). Following this report, the visual fields were examined by accurate

perimetric methods and a bitemporal hemianopia for small objects and for color was demonstrated. Specific questioning regarding possible symptoms from this presumably extensive chiasmal lesion gave negative results. The patient could not recall any noticeable visual disturbances, headache, dizziness, or other symptoms which could be attributed to increased intracranial pressure. The vomiting, which was a prominent symptom, had never been of the projectile type.

Two determinations were made of the basal metabolic rate; the first (performed on Dec. 29, 1934) was −23%, and the second (performed on Jan. 5, 1935) was −22%. The blood cholesterol, on Jan. 5, was 175 mg., the blood lecithin 248 mg. The total volume of plasma was 49 cc. per kilo, the total blood volume 72.8 cc. per kilo. The blood calcium and phosphorus readings were found to be 11.6 and 1.3 mg.% respectively. An analysis of the gastric content following the intramuscular injection of histamine was made on Jan. 5, 1935, and repeated on Jan. 9 using epinephrine as a stimulant. The results are shown in Table 2. It is interesting that larger volumes of secretion and even higher values for gastric acidity were obtained following the administration of epinephrine.

TABLE 2.—RESULTS OF ANALYSIS OF GASTRIC CONTENTS.

	January 5.		
Specimen.	Amount, cc.	Free HCl, units.	Total acid, units.
1	20	24	54
2	35	66	80
6.7 mg. histamine injected intramuscularly			
3	40	84	98
4			
5	50	80	92
6	35	90	100
7	45	110	120
8	20	114	122
Total secretion in 80 minutes, cc.	245		

	January 9.		
Specimen.	Amount, cc.	Free HCl, units.	Total acid, units.
1	120	86	100
1	30	100	112
3	30	76	86
4	20	86	92
9 minims epinephrine hydrochloride injected intramuscularly			
5	75	104	114
6	50	110	118
7	50	110	124
8	45	132	138
Total secretion in 80 minutes, cc.	420		

Roentgenologic examination of the stomach revealed a duodenal ulcer. This was regarded as the probable explanation of the patient's abdominal pain and subsequent experience with ulcer therapy confirmed this opinion. Roentgenologic examination of the colon was reported as giving negative results, although the organ appeared to be rather large and atonic.

It seemed necessary that the pituitary tumor should receive attention first, particularly since it was beginning to cause defects in the visual fields and since it was also considered to be primarily responsible for the patient's hypoglycemia and cachexia; however, the multiplicity of abnormal changes which this patient presented made evident the added risk that would attend

FIG. 1.—Enlargement of sella turcica with thinning of posterior clinoid processes.

an operation of this type. For this reason, further laboratory and therapeutic measures were carried out with the hope that some means might be discovered to raise the blood sugar to a higher, and possibly a safer, level for the operative procedure or to counteract any crisis that might occur postoperatively. Anterior pituitary extract was used, with negative results; the effect of epinephrine was also studied (Table 3). While epinephrine produced a temporary increase in the value for blood sugar, suprarenal cortical hormone had no effect on the patient's general condition or on the value for blood sugar, as will be noted later.

TABLE 3.—EFFECTS OF EPINEPHRINE ON THE BLOOD SUGAR.

Time, A.M.	Blood pressure. Systolic.	Blood pressure. Diastolic.	Blood sugar, mg. per 100 cc.
10.30	120	68	38
9 minims epinephrine injected subcutaneously at 10.30			
10.35	136	70	
10.45	..	..	55
10.50	130	70	
10.55	..	..	62
11.00	122	66	
11.03	..	..	62

The final preoperative diagnosis was pituitary adenoma, with involvement of the optic chiasm, secondary hypoglycemia, eunuchoidism and duodenal ulcer. On the 15th day after admission, right transfrontal craniotomy was done for the removal of the pituitary tumor and a large, cystic, degenerating pituitary adenoma was exposed. The tumor was shaped like a mushroom (Fig. 2), the stem rising between the optic nerves. The dome-like portion was cystic and had compressed the third ventricle; the base rested on the optic chiasm. The cyst was emptied of about 10 cc. of yellow fluid. Only a portion of the tumor was removed as it seemed to infiltrate the adjacent structures and, because of its vascularity, it seemed better to treat it postoperatively with radiotherapy. A transfusion of 500 cc. of blood was given during the course of the operation. Microscopically, the tumor proved to be a chromophobe adenoma.

There was surprisingly little reaction to the operation and the patient's convalescence was relatively uneventful; by 8 P.M. on the day of operation he was asking questions and was able to move all his extremities. His axillary temperature rose to 100.3° F. the day following the operation, after which it remained normal.

The patient was watched closely for any symptoms of hypoglycemia or other symptoms following operation, but none appeared. Estimations of blood sugar and chlorides were made every 6 or 8 hours postoperatively during the first 2 days and daily thereafter. Intravenous injections of 5 cc. of suprarenal cortical hormone, as prepared by Kendall, were given in the evening of the first and second days following operation. Following this he received from 5 to 20 cc. of the suprarenal cortical hormone intramuscularly for 3 days. This was without apparent effect on the patient's general condition or on the value for blood sugar.

Sweetened fruit juices and a diet high in carbohydrate were given on the second day after operation, and this was tolerated fairly well until the fifth day, when the patient began to vomit. He was then placed on a bland ulcer diet and remained comfortable; no alkalies or sedatives were necessary to control the digestive symptoms. The patient was transferred to the Radiologic Section on Jan. 21, 1935, and received high voltage therapy for 5 days over the lower frontal, occipital, right and left temporal, and vertex regions of the head. He had considerable reaction from these treatments, became quite nauseated, and vomited several times.

Neurologic and ophthalmoscopic examinations were made just prior to the patient's final dismissal, on Jan. 25, 1935, but the results were no different from those obtained before operation. At the time of dismissal his general condition was good. The partial removal of the pituitary tumor and Roentgen therapy of the pituitary area did not have any apparent effect in restoring the blood sugar to a normal value. The patient died about 2 months following dismissal. Details of his final illness were not obtained, death presumably occurring from exhaustion and cachexia.

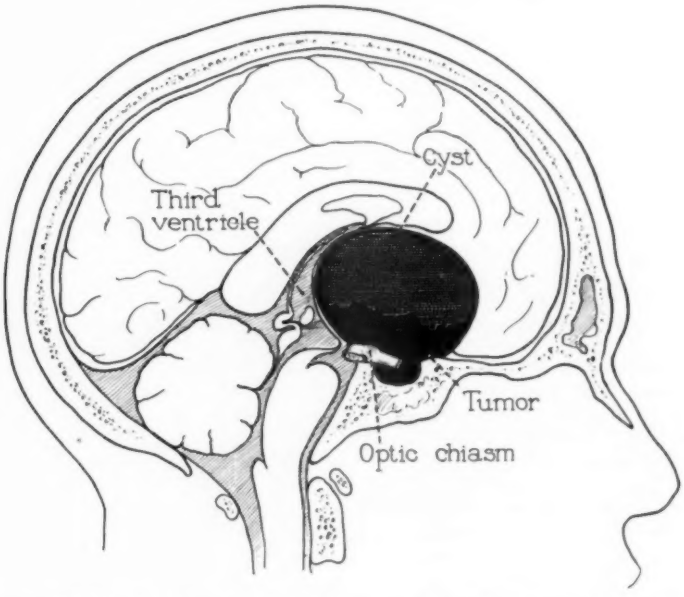

FIG. 2.—Situation of tumor and its relationship to hypophysis and third ventricle.

In reviewing this case it seems probable that all of the patient's symptoms were secondary to the presence of the original neoplasm, which undoubtedly arose from the anterior lobe of the hypophysis. It is further believed that these symptoms were in general referable to the destruction of the anterior lobe and suppression of its hormonal activity. The lethargy, depression, and general decline in health were thought to be due to the general depressing effects of loss of anterior lobe secretions on tissue metabolism; the genital atrophy and the abnormalities of the secondary sexual characteristics were thought to be due to the loss of the gonadotropic hormone and the chronic hypoglycemic state was thought to be due to the loss of the diabetogenic hormone. The low basal metabolic rate may have been due in part to malnutrition and inactivity, or it may be explained on the basis of failure of the anterior lobe to provide the proper stimulus for thyroid function. The duodenal ulcer, which produced symptoms of unusual severity, is comparable to the peptic ulcers which follow lesions of the third ventricle.

Brain Lesions and Their Relation to Peptic Ulcer. Rokitansky (1841–1846) appears to have been the first to regard ulcerative processes of the gastro-intestinal tract as being of neurogenic origin. Since then several other investigators have reported cases of gastric and duodenal ulceration associated with intracranial lesions.[1,2,8,11,14,21] Cushing (1932),[5b] in an excellent review of the subject both from the clinical and experimental aspects, again aroused interest in the occurrence of gastric and duodenal ulceration associated with lesions of the brain. Comroe[4] (1933) reported 2 cases of pituitary tumor associated with peptic ulcer, and Swan and Stephenson[19] have recently reported a case of basophilic adenoma of the pituitary in which death occurred after hemorrhage from a large penetrating gastric ulcer.

One may summarize the whole matter by stating that there is both clinical and experimental evidence to suggest that intracranial lesions may produce changes in the gastro-intestinal tract, and that these changes may take the form of both acute and chronic peptic ulceration. In the case reported herein there can be little doubt that the hypophyseal neoplasm antedated the formation of the duodenal ulcer, but the etiologic importance of the former in the production of ulcer can only be surmised.

Hypoglycemia of Hypophyseal Origin. The occurrence of hypoglycemia in the case herein reported was perhaps the most striking single clinical feature. The extremely low values for blood sugar, with the absence of symptoms referable to such a condition, the lack of response to high carbohydrate diets and to intravenous infusions of glucose and epinephrine, and the persistence of the low value for blood sugar, even after removal of a portion of the tumor, are particularly worthy of comment. We were unable to find the report of a single case in the literature on pituitary tumor associated with a value for blood sugar as low as 0.30 mg. % in the absence of hypoglycemic symptoms.

Cushing (1912)[5] was probably the first to report a proved case of hypoglycemia associated with pituitary tumor. Wilder (1930)[20] reported 2 cases in which there were neuropsychiatric symptoms and a periodic loss of consciousness associated with the periods of hypoglycemia. Enlargement of the sella turcica was demonstrated in both of these cases and one patient had the appearance of being mildly acromegalic. Discussing the relation of pituitary lesions to hypoglycemia, Wilder cited cases of this type previously reported by Frazier,[7] Jacob,[10] Pribram,[15] Stenström[18] and Meng.[13] There has been much experimental evidence in support of the theory that the pituitary gland plays a part in carbohydrate metabolism. The reader is referred to the excellent reviews of this subject by Houssay,[9] Long,[12] Russell[17] and Colwell.[3] Kepler and one of us[6] (M. P. F.) are studying the relation of glucose tolerance curves to pituitary tumors; the results of this study will be reported in a subsequent publication.

Studies of blood sugar and glucose tolerance tests unfortunately could not be carried out in our case long after operation and Roentgen therapy; however, the association of an anterior hypophyseal lesion, cachexia, and a persistent and severe but asymptomatic hypoglycemia adds another example to the series collected by Wilder. The mechanisms involved are obscure and the best explanation at present available is that there may be some interference with the relations between the diabetogenic hormone of the anterior hypophysis and insulin.

Relation of Hypophyseal Lesions to Basal Metabolism. The low metabolic rate in our case has been mentioned previously and needs no additional comment, since the finding of a low rate is a very common accompaniment of hypophyseal lesions and one which has been discussed frequently. Such lowered states of metabolism are particularly common in pituitary cachexia, such as this patient presented; they may represent, in such instances, not only an endocrine effect, but secondary changes in nutrition.

Summary. The presenting symptoms of a patient with a large cystic chromophobe adenoma of the anterior hypophysis were those of penetrating duodenal ulcer. Such a lesion was demonstrated roentgenologically and symptomatic relief was obtained on ulcer management. The patient also had definite hypoglycemia; the level of the blood sugar was not permanently elevated by a high carbohydrate diet, intravenous infusions of glucose, suprarenal cortical hormone, or anterior pituitary extracts. Epinephrine produced a slight temporary increase. The blood sugar was not affected by removal of a portion of the tumor and subsequent radiotherapy. Cachexia, eunuchoidism, and lowered metabolism were additional features. The probable relation of these symptoms to the original hypophyseal lesion is discussed.

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MINERAL APPETITE OF PARATHYROIDECTOMIZED RATS.*

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Biochemical studies have demonstrated the existence of marked disturbances in the mineral metabolism of parathyroidectomized animals. It has been shown that the serum calcium falls to a very low level and that the accompanying tetany and other deficiency symptoms may be eliminated by the administration of calcium (MacCallum and Voegtlin;[7] Lieberman and Szurek[4]). Evidently, parathyroidectomized animals have an increased calcium need.

In a previous study, it was reported that, given free, but not forced access to calcium lactate solution (2.4%), parathyroidectomized rats ingested large quantities and thereby seemed to make an effort to satisfy their increased calcium need (Richter and Eckert[8]). Of the 18 rats tested, 17 drank an average of 3.9 times more calcium lactate solution after parathyroidectomy than before. Parathyroid implants made to the anterior chamber of the eyes quickly reduced the calcium lactate intake to its normal level.

Although it seemed very likely from these experiments that parathyroidectomized rats have a calcium craving, a definite conclusion to this effect could not be drawn without showing that the rats have an increased appetite for other calcium solutions besides the lactate. The first part of the following experiments deals with the appetite of parathyroidectomized rats for calcium gluconate, calcium acetate, and calcium nitrate.

Biochemical studies have also shown that removal of the parathyroids results in a marked phosphorus retention (Greenwald and Gross;[3] Greenwald;[2] Weaver and Reed;[12] Esau and Stoland[1]). Phosphate administered in the diet in large amounts increases tetany (Salvesen, Hastings and McIntosh[9]). Experiments were performed to determine whether this phosphorus retention has any effect on phosphate appetite, whether the parathyroidectomized rats exhibit a phosphate aversion or craving.

For some time it has been known that parathyroid tetany improves under treatment with strontium and magnesium salts (Luckhardt, Waud and Brannon;[6] Swingle and Wenner[11]). Experiments were undertaken, therefore, to determine whether parathyroidectomy increases the appetite for strontium and magnesium.

* These experiments were supported by grants from the Rockefeller Foundation and from the Committee for Research in Endocrinology of the National Research Council.

Methods. The animals were kept separately in cages, $7\frac{3}{4}$ by $12\frac{1}{2}$ by 10 inches, containing a food cup and, in most of the experiments, only 2 inverted 100 cc. graduated bottles. One bottle contained tap water, the other a calcium, strontium, magnesium or phosphate solution. Daily records of the fluid intake were made for several weeks before operation and for at least 40 days afterwards. Rats on the calcium and phosphate choices received the standard McCollum diet but minus the 1.5% calcium carbonate; rats on the strontium and magnesium choices received the standard McCollum diet with the calcium carbonate. Rats on the multiple choice of mineral solutions received a low mineral diet, kindly furnished us by Dr. W. B. Cox of the Mead Johnson Laboratories.

The operative technique requires no detailed comment beyond the statement that an effort was made not to rupture the parathyroid capsule nor severely injure the thyroid. Only one pair of parathyroid glands was found in each animal.

The following solutions were used in these experiments:

	Per cent.		Per cent.
Calcium lactate	2.4	Sodium lactate	4.0
Calcium gluconate	0.3	Potassium chloride	2.0
Calcium nitrate	0.5	Strontium chloride	0.02
Calcium chloride	1.0	Strontium lactate	0.02
Calcium acetate	0.01	Magnesium chloride	0.5
Sodium phosphate (dibasic)	4.0	Magnesium lactate	0.02

The selection of the concentration of the solutions depended on the following considerations: the solutions had to be strong enough to permit the rat to distinguish them easily from tap water and yet not so strong that the rats refused them entirely. A previous paper contains the details of the process used to determine these concentrations (Richter and Eckert,[8]). The apparent preference of the rats for solutions of these concentrations remains unexplained.

Results. *Appetite for Calcium.* It was found that parathyroidectomized rats have an increased appetite for solutions of calcium gluconate, nitrate, and acetate as well as lactate. Figure 1 shows the records of 3 typical animals. The calcium gluconate intake of the first animal increased from a level of approximately 10 cc. per day before parathyroidectomy to a level near 28 cc. 20 days after. The calcium nitrate intake of the second animal increased from a level near 5 cc. per day to a peak of 29 cc. 39 days after parathyroidectomy. The calcium acetate intake of the third animal increased approximately the same amount.

Table 1 summarizes the results. It includes also data obtained from 27 animals on a calcium lactate choice. All except one of these 27 rats showed an increased calcium lactate intake. The average daily intake for the group increased from 4.6 cc. for the 10-day period immediately preceding parathyroidectomy to 17.7 cc. during the 20 to 30-day postoperative period. The ratio of the increase was 3.84.

Three rats on a calcium acetate choice showed an increased intake. The average daily intake increased from 3.6 cc. to 11.2 cc., giving a ratio of 3.11. Three out of 4 rats showed a markedly increased

calcium gluconate intake. Three rats on calcium nitrate choice showed a smaller but definitely increased intake.

TABLE 1.—CALCIUM (SINGLE CHOICE).

McCollum food without calcium carbonate.

Solution.	No. of animals.	Number showing.			Average daily intake in cc.		Average ratio 20–30 days after: 10 days before.
		Increased intake.	Unchanged intake.	Decreased intake.	10 days before parathyroidectomy.	20–30 days after parathyroidectomy.	
Calcium lactate, 2.4% .	27	26	1	0	4.6	17.7	3.84
Calcium acetate, 0.01% .	3	3	0	0	3.6	11.2	3.11
Calcium gluconate, 0.3%	4	3	1	0	7.1	10.4	1.46
Calcium nitrate, 0.5% .	3	3	0	0	3.8	4.9	1.29

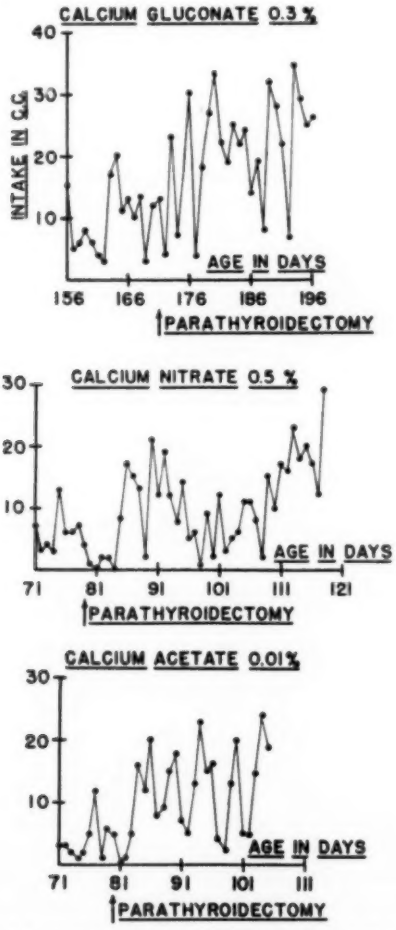

FIG. 1.—Records of 3 typical animals showing daily intake of various calcium salts before and after parathyroidectomy.

These experiments show that parathyroidectomized rats have an increased calcium craving.

Appetite for Phosphate. In the first part of these experiments 6 rats were each given access to 3 bottles, containing tap water, calcium lactate, 2.4% solution, and dibasic sodium phosphate, 4% solution, respectively.

After parathyroidectomy the rats drank more of the calcium lactate and less of the dibasic sodium phosphate solution. Table 2A summarizes the results. Five of the 6 rats showed an increased calcium lactate intake, giving a ratio of 2.63. Five out of 6 decreased their dibasic sodium phosphate intake, giving a ratio of 0.43.

In the second part of the phosphate experiment, 6 rats fed a low mineral diet (Cox) each had access to 6 bottles containing tap water, calcium lactate, dibasic sodium phosphate, calcium chloride, potassium chloride, and sodium lactate, respectively. Figure 2 presents a typical record of one animal showing the daily intake of each of these solutions for 17 days before parathyroidectomy and for 43 days afterwards. The calcium lactate intake increased from a level of 1 to 2 cc. per day before parathyroidectomy to a level of 30 cc. 40 days later. The increase occurred almost at once after parathyroidectomy, reaching 18 cc. on the second day. In sharp contrast the dibasic sodium phosphate intake decreased from an average level of 7 cc. to a level of 3 cc. Sodium lactate intake also decreased, while the intake of calcium chloride and potassium chloride remained unchanged.

TABLE 2A.—CALCIUM AND PHOSPHATE CHOICE.

Full McCollum Diet (6 Animals).

Solution.	Number showing.			Average daily intake in cc.		Average ratio 20–30 days after:10 days before.
	Increased intake.	Unchanged intake.	Decreased intake.	10 days before parathyroidectomy.	20–30 days after parathyroidectomy.	
Calcium lactate, 2.4%	5	0	1	4.9	12.9	2.63
Sodium phosphate, 4% (dibasic)	0	1	5	6.8	2.9	0.43
Water	1	0	5	33.0	26.1	0.79

TABLE 2B.—MULTIPLE MINERAL CHOICE.

Cox's Low-mineral Diet (6 Animals).

Calcium lactate, 2.4%	5	1	0	7.3	21.9	3.0
Potassium chloride, 2%	3	2	1	1.4	1.0	0.75
Sodium lactate, 4%	2	0	4	3.0	3.0	1.0
Calcium chloride, 2%	1	5	0	0.5	0.5	1.0
Sodium phosphate, 4% (dibasic)	0	0	6	5.5	1.9	0.35
Water	0	1	5	22.3	10.0	0.45

Table 2*B* summarizes the results for 6 rats. The average daily intake of calcium lactate increased from 7.3 cc. for the 10-day period preceding parathyroidecomy to 21.9 cc. for the 20 to 30-day post-

operative period, giving a ratio of 3.0 which is almost the same as that obtained in the calcium experiments described above. At the same time, the average daily dibasic sodium phosphate intake decreased from 5.5 cc. to 1.9 cc., giving a ratio of 0.35. The average daily intake of potassium chloride, calcium chloride, and sodium lactate remained practically unchanged.

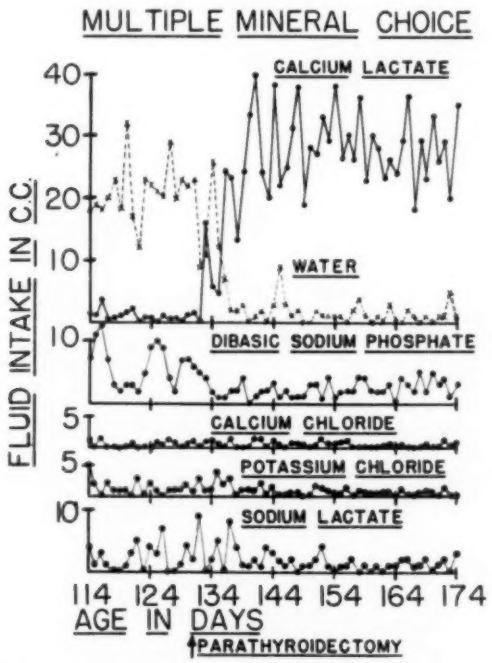

FIG. 2.—Record of a typical animal showing daily intake of 5 salts and water before and after parathyroidectomy.

These experiments show that a phosphate aversion apparently accompanied the calcium craving.

Appetite for Strontium and Magnesium. It was found that the parathyrectomized rats have an increased appetite also for strontium and magnesium solutions. Figure 3 shows 2 typical records. The first record presents the intake curves for water and strontium chloride for 18 days before parathyroidectomy and 42 days afterwards. During the 18-day period the daily intakes of water and the strontium solution were nearly the same, averaging 18 to 20 cc. On the fourth day after parathyroidectomy the intake of strontium chloride increased sharply to 36 cc. while the water intake decreased to 4 cc. Parathyroid implants made to the anterior chamber of the eyes 25 days after parathyroidectomy caused the strontium chloride

intake to decrease and the water intake to increase sharply within 8 days. The magnesium chloride intake of the other animal increased from an average daily intake of 5 cc. before parathyroidectomy to a level near 40 cc. 30 days afterwards.

Table 3 summarizes the results. Three out of 4 rats showed an increased strontium chloride intake. The average daily intake increased from 8.2 cc. for the 10 days preceding parathyroidectomy to 17.2 cc. in the 20 to 30-day period afterwards, giving a ratio of 2.10. The magnesium chloride intake showed a similar increase. The increase in the intake of the strontium lactate and magnesium lactate solutions was less marked.

TABLE 3.—OTHER MINERALS (SINGLE CHOICE).

Full McCollum Diet.

Solution.	No. of animals.	Number showing.			Average daily intake in cc.		Average ratio 20–30 days after:10 days before.
		Increased intake.	Unchanged intake.	Decreased intake.	10 days before parathyroidectomy.	20–30days after parathyroidectomy	
Strontium chloride, 0.02%	4	3	1	0	8.2	17.2	2.10
Strontium lactate, 0.02% .	3	2	1	0	7.1	8.8	1.24
Magnesium chloride, 0.5%	3	3	0	0	11.2	23.1	2.06
Magnesium lactate, 0.02%	4	1	3*	..	2.7	3.9	1.44

* All died of tetany within 24 hours.

The results show that parathyroidectomized rats apparently have an increased appetite for strontium and magnesium as well as for calcium.

Discussion. These experiments indicate that, given an opportunity, parathyroidectomized rats, like adrenalectomized rats, make mineral selections which are conducive to the maintenance of a normal physiological equilibrium. Adrenalectomized rats, given a saltless diet and without access to any salt solution, suffered 100% mortality, dying after an average of 9 days. When the rats were given access to a salt solution, the mortality decreased sharply and most of the animals continued to grow at the normal rate. Given access to several mineral solutions containing most of the essential electrolytes, the mortality decreased to zero, and all rats showed normal growth. Obviously the rats made beneficial selections.

Parathyroidectomized rats, kept on a low calcium diet (McCollum diet without calcium carbonate) and without access to calcium, showed a 52% mortality. Thirteen out of 25 rats died, in most instances within the first 24 hours. All of the surviving rats showed tetany for at least 10 days and lost weight for 10 to 20 days. However, given access to calcium solutions (lactate, acetate, gluconate, and nitrate), parathyroidectomized rats made selections which reduced the mortality to zero, greatly reduced the tetany, and either eliminated or reduced the weight loss.

The parathyroidectomized rats clearly indicated an increased appetite for calcium, especially for calcium lactate. It has been reported that calcium lactate is more efficient in relieving symptoms of tetany in animals and humans than any other calcium salt given orally, provided it is given with water (Luckhardt and Goldberg[5], Wilson[13]).

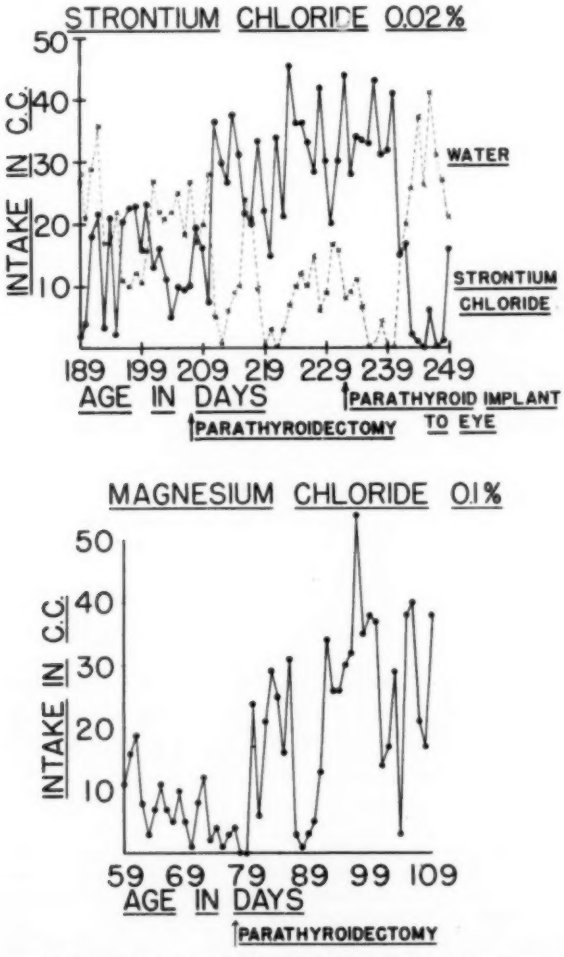

FIG. 3.—Records of 2 typical animals showing daily intake of strontium chloride and magnesium chloride before and after parathyroidectomy.

The increased appetite for strontium and magnesium is of special interest because of the close atomic relation of these two elements to calcium.

It is even possible that parathyroidectomized rats may have an

increased appetite for other minerals. Numerous single and multiple choice experiments made with sodium and potassium solutions, however, did not reveal cravings for these minerals.

The aversion for phosphate has already been described by Shelling.[10] He states that parathyroidectomized rats will display an appetite for diets rich in calcium and low in phosphorus, but will refuse to partake of diets low in calcium or high in phosphorus. Moreover, it appears that a high phosphate diet is refused only when the phosphate is in a form that the animal can use, and hence retain. Diets in which the phosphate is in an unusable form (the metaform) are not refused. Evidently the phosphate retention plays an important rôle in the appetite of parathyroidectomized animals. The present study confirms these findings. The craving for calcium and the aversion toward phosphate are no doubt results of the decreased serum calcium and the phosphate retention.

At the present time, it would appear that the selections made by the rats may depend, not on a trial and error process, but on chemical changes in the taste mechanisms in the oral cavity, making the calcium more desirable after parathyroidectomy than before. The craving for calcium may almost be considered as a tropism response. Section of the taste nerves should give an answer to this question.

Summary. 1. Parathyroidectomized rats showed a markedly increased appetite for calcium solutions (lactate, acetate, gluconate, and nitrate) and an aversion toward dibasic sodium phosphate solution.

2. Parathyroidectomized rats also showed an increased appetite for strontium and magnesium salt solutions.

3. These results agree with the present knowledge concerning the disturbed calcium and phosphorus metabolism after parathyroidectomy.

4. The decreased mortality and alleviation of deficiency symptoms of parathyroidectomized rats given access to calcium solutions add further proof that rats have an ability to make selections conducive to their well-being.

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ADRENAL APOPLEXY IN A MAN OF 72 FOLLOWING IDIOPATHIC THROMBOPHLEBITIS OF THE ADRENAL VEINS.

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MASSIVE bilateral hemorrhage into the adrenal glands is uncommon, and in adults extremely rare. Less than a dozen cases above the age of 20 years have been recorded and thus far none over the age of 55. A number of very complete reviews and discussions of the syndrome associated with massive adrenal hemorrhage has appeared recently[1,3,5–8,11] The purpose of the present communication is to record the clinical picture and post-mortem findings in a man who developed this syndrome at the age of 72.

Case Report.—M. F. (BIH 19213), male, entered the hospital on May 14, 1934, complaining of excruciating upper abdominal pain of 24 hours' duration. His family history was negative. Past history revealed pneumonia and typhoid fever 50 years previously. About 2 years before admission he developed a slightly productive cough and 10 months before admission had a few small hemoptyses. He was seen in the Out-patient Department where a diagnosis of carcinoma of the lung was established. He received no treatment for this condition. In the 2 years preceding admission he had also been troubled by chronic constipation and bleeding piles. On May 14, 1934, at about noon the patient was suddenly seized with a severe stabbing pain in the midline above the umbilicus. He vomited 4 or 5 times during the next few hours, the vomitus consisting of mucus and clear colorless fluid. The pain persisted until the time of admission in spite of the subcutaneous injection of morphia by his local physician.

Physical examination revealed a poorly nourished old man writhing in pain. The right chest was dull anteriorly in its upper portion and breath sounds were diminished over this area. A few fine râles were heard over this area also, and numerous crackling râles were audible at the bases. The abdomen was board-like, with exquisite tenderness and rebound tenderness above the umbilicus. The temperature was 98.8° by rectum, pulse 104, respirations 32, and blood pressure 140 mm. of mercury systolic and 95 mm. of mercury diastolic. The white blood cell count was 20,000 per c.mm.

A diagnosis of ruptured hollow viscus was made and the patient taken to the operating room immediately. Under local anesthesia supplemented with gas oxygen and ether the abdomen was opened. Careful exploration revealed no abnormality of any sort within the peritoneal cavity and the abdomen was closed. After operation the patient's blood pressure was 110 mm. of mercury systolic and 60 mm. of mercury diastolic. These soon fell to 70 and 50 respectively. The patient rapidly failed in spite of supportive treatment, developing air hunger and cyanosis. He died 10 hours after operation.

Autopsy (A–34–61, Drs. Fienberg and Frehling). The adrenal glands were swollen and, particularly in and about the medulla, markedly hemorrhagic. There was also considerable hemorrhage into the capsules of both glands.

The other gross findings included a neoplastic nodular mass infiltrating

almost all of the right upper lobe of the lung, and extending into the mediastinum where it impinged on and invaded the wall of the superior vena cava and the right subclavian vein. These vessels contained small nonoccluding thrombi over the invading tumor tissue. The coronary arteries and aorta showed a slight amount of arteriosclerosis. A few tiny patches of extravasated blood were found in the gastric mucosa and the renal pelves. No other thrombosed veins were found anywhere. Blood culture was negative.

Microscopic examination of the adrenal glands showed the large and small veins to be occluded by recent ante-mortem thrombi. The walls of these vessels showed moderate to marked edema and acute inflammatory cell reaction. There was marked hemorrhage into the medulla and surrounding tissue entirely obliterating the normal histology. The cells of the cortex in many areas were completely necrotic; in others, marked vacuolization of the cytoplasm and pyknosis of the nuclei were predominant. There was acute inflammatory cell infiltration within the gland and also external to the capsule. The arteries and arterioles were free of thrombi.

The rest of the microscopic examination confirmed the gross findings and revealed in addition scattered fibrotic patches in the kidneys, and slight necrotic changes and fibrin deposit in the splenic corpuscles.

Discussion.—Massive bilateral adrenal hemorrhage occurs in a variety of diseases. It has been noted in the neonatal period, in septicemias of various sorts, usually meningococcic or pneumococcic, in fatal diphtheria, following trauma, in severe burns, in purpura, and in thrombophlebitis of the adrenal veins of unknown etiology.[1,3,5–8,11] Most of the cases recorded in the literature have occurred in children with fulminating septicemia. The symptoms associated with the syndrome depend to a considerable degree on the underlying pathologic process. Thus when a septicemia is responsible for the process the patients exhibit severe purpura, high fever and signs of meningitis, in addition to the signs and symptoms due to the adrenal hemorrhages themselves and the syndrome is called the Waterhouse-Friderichson Syndrome.[1,6,8] In this syndrome, the massive bilateral adrenal hemorrhages are usually not associated with venous thrombosis but are due to arterial or capillary embolization. In adults, pain is frequently the presenting symptom. The pain may occur over the costovertebral angles, or, as in the case recorded here, over the upper abdomen. In the case described in this paper, the abdominal pain was excruciating and was accompanied by board-like rigidity of the abdominal wall. The diagnosis of perforated abdominal viscus was not confirmed by exploratory laparotomy and subsequent autopsy. The cases of Barsoum[2] and of Hall and Hemken[5] were also subjected to laparotomy because of the nature and distribution of the pain. In adults, the underlying cause is usually thrombophlebitis of the adrenal veins of unknown etiology. In occasional instances the patient may have peripheral thrombophlebitis as in the case reported by Pearl and Brunn.[7] In all cases, no matter what the etiology, shock, usually rapidly progressive, is a prominent manifestation and is the cause of death. The occurrence of shock following the sudden destruction of both

adrenal glands is to be expected from what is known of the physiology of those organs.

The factor responsible for the development of the adrenal vein thrombophlebitis in the case here reported, as in other cases in the literature, is unknown. No connection between the thrombophlebitis and the carcinoma of the lung could be established. This type of case is best regarded as one of that group of instances of visceral thrombophlebitis of unknown etiology which may also localize in the portal vein,[10] inferior vena cava,[4] hepatic veins,[9] renal veins,[4] or mesenteric veins,[12] each giving rise to a typical symptom complex depending on the organs involved.

Summary.—A case of idiopathic thrombophlebitis of the adrenal veins with bilateral adrenal apoplexy occurring in a man of 72, suffering from carcinoma of the lung is reported. The clinical picture of this syndrome is discussed. It is pointed out that this condition falls into the group of syndromes due to visceral thrombophlebitis which may involve the veins of any abdominal viscus, giving rise to a variety of signs and symptoms depending on the organ involved.

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REPORT OF 50 CASES OF ACUTE LOBAR PNEUMONIA IN ADULTS TREATED WITH SULPHAPYRIDINE.

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In the Henry Ford Hospital over the preceding 8 years 678 cases of lobar pneumonia have been treated by all methods, both with and without serum. Of these, 253 have died (37%). These patients were all adults, with no exceptions made on the basis of day of disease, type of pneumococcus or condition on admission.

During the past winter 50* unselected, consecutive adult cases of

* Since the above report was prepared, 20 additional cases of lobar pneumonia in adults have been treated with sulphapyridine. There were 2 deaths. The mortality for the entire 70 cases was therefore 8.5%.

lobar pneumonia were treated with sulphapyridine. In this series there were 4 deaths, a mortality of 8%. Only those patients who presented history and physical findings considered typical of lobar pneumonia were included in this series, and all had from one to several chest Roentgen ray examinations. Blood cultures were made in all cases.

TABLE 1.—PNEUMOCOCCUS TYPING OF PNEUMONIA CASES TREATED WITH SULPHAPYRIDINE.

Type.	No. of cases.
I	4
II	5
III	5
IV	5
V	2
VII	10
VIII	2
XVIII	1
	34

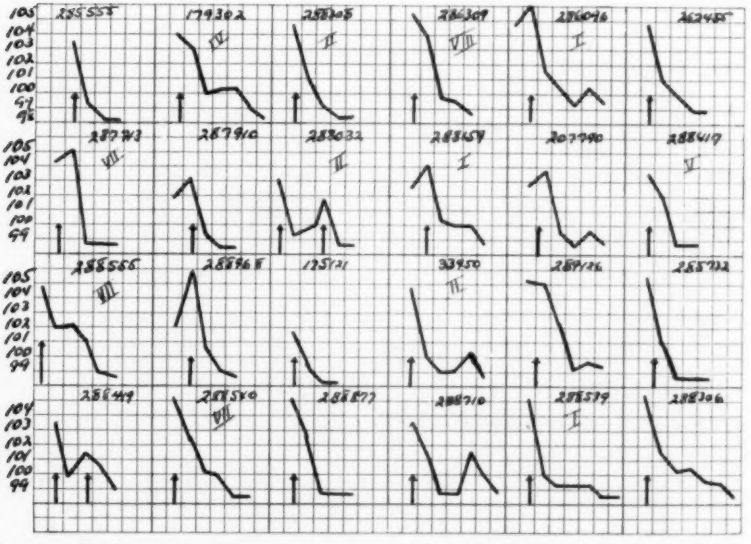

FIG. 1.—Maximum temperature. Arrow indicates beginning of sulphapyridine in 24 cases. Each space = 1 day.

No pneumococcus typing could be determined by our methods in 15 of the cases. In this series only 5 patients received anti-pneumococcus serum. All patients received sulphapyridine. The exhibition of sulphapyridine did not vary materially. Routinely, after the clinical diagnosis was established and sputum and blood cultures obtained, an initial dose of 3 gm. of the drug was given, followed in 2 hours by 2 gm. and then 1 gm., every 4 hours until a total of from 15 to 25 gm. had been administered, or until the temperature reaction was favorable.

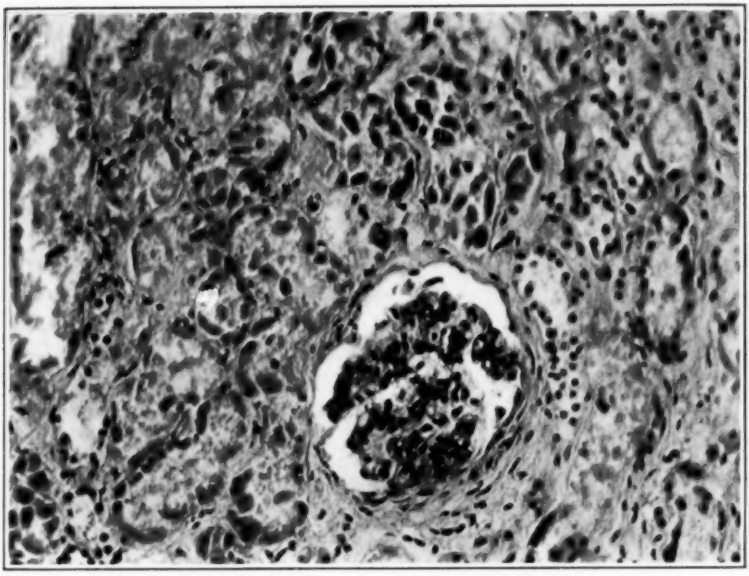

FIG. 2.—Case 1. Kidney (medium power), showing tubular necrosis in localized area about glomerulus. Tubular epithelium stains uniform pink and is desquamating.

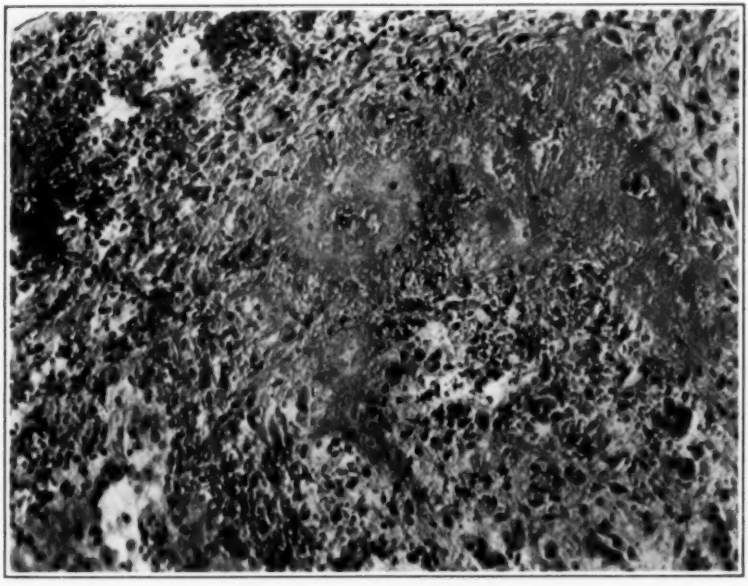

FIG. 3.—Case 1. Adrenal (medium power), showing areas of necrosis in cortex surrounded by areas of hemorrhage.

The common temperature response to the drug is exemplified by the accompanying chart of 24 sulphapyridine-treated cases. Prompt and abrupt defervescence was the rule; and failure to develop this typical response led to the justified suspicion that a non-pneumococcic infection might be the causative agent in 3 cases. Two of these at autopsy proved to be instances of staphylococcus pneumonia, and 1 a tuberculous pneumonia.

Only 1 pneumococcus complication occurred, an instance of empyema—the patient making a recovery with intercostal drainage.

As with other investigators, we found nausea to be the common reaction of practically all patients treated with the drug. This was in many instances severe, but in no case did its presence prevent the use of the drug.

In many instances, large jagged arrowhead-shaped crystals of sulphapyridine were found in the urine toward the end of the drug therapy, but no evidence of renal damage was encountered save in 1 instance (Case 1).

No effect was seen on the blood picture. Cyanosis was not thought to be present in our cases in any greater degree than in any other similar group of lobar pneumonias treated by other methods.

Four deaths occurred as follows:

Case 1.—G. G. white female, aged 54. Semicomatose 8th day of disease, Type III pneumococcus (sputum). Right lower lobe involved. Urine showed 3+ albumin and occasional red cell. After 8 gm. of the drug had been administered, developed anuria and treatment was stopped. Temperature had fallen with treatment and remained at low level several days. Renal function returned in 2 days but a new consolidation developed and death occurred without further specific treatment.

Autopsy (Dr. Frank Hartman) showed a resolving pneumonia of the right lower lobe and a fresh consolidation of the left upper lobe. The kidneys showed acute toxic nephritis with both tubular degeneration and focal necroses. Focal necroses were also present in the adrenals.

Case 2.—I. D., white male, aged 76. Sputum and blood culture showed Type II pneumococcus. Treated with serum with marked thermal reaction and then both serum and sulphapyridine. Death on the 9th day.

Case 3.—F. P., white male, aged 64. Admitted 3d day. Sputum and blood both positive for Type IV pneumococcus. Showed satisfactory temperature response but after 18 hours of normal temperature developed ventricular tachycardia (E. K. G.) and died during this attack.

Case 4.—M. B., white male, aged 51. Admitted 7th day. Sputum and blood both positive for Type VII pneumococcus. Also had syphilis, was a chronic alcoholic and was in auricular fibrillation with a ventricular rate of 160. Died 18 hours after admission.

Summary. To add to the existing records of the sulphapyridine treatment of acute lobar pneumonia in adults, 50 unselected consecutive cases so treated are presented with a mortality of 8% contrasted with a previous mortality in a series of 678 cases of 37%.

Aside from nausea, only one toxic effect was encountered thought due to the drug—an instance of acute toxic nephritis and focal necrosis in the adrenal, confirmed by autopsy.

THE RESULTS OF SULFAPYRIDINE THERAPY IN 400 CASES OF TYPED PNEUMOCOCCIC PNEUMONIA.*

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In previous reports[7,8] we have reviewed the earlier experimental and clinical data pertaining to the use of sulfapyridine in pneumococcal infection; in the second of these,[8] we reported our clinical experience with sulfapyridine therapy in 100 cases of pneumococcic pneumonia. These 100 cases are included in the 400 cases reported in this paper. Since their publication, confirmatory experimental work in the laboratory and clinical results with this drug have been reported from widely separated sources.[1-3,5,9,11,16,18] In the main, the mortality, toxic reactions, and complications in our clinical studies have been the same as in other clinics. The purpose of this paper is twofold, to report the results of 400 typed cases† of pneumonia treated in Philadelphia with sulfapyridine, and to present certain observations made while using the drug. We have studied 100 additional cases in which no typable pneumococcus could be obtained, but have not included data on these cases in this analysis of dosage, therapeutic results, influence of the drug on the course of the disease, complications, and toxic effects. In these patients, the diagnosis of pneumonia was definitely established by clinical and laboratory studies. Roentgen examinations were made in 66% of the cases and blood cultures were taken in 94%, although some of the cultures were not taken until after treatment had been started. All but 7 of the patients were followed personally by the authors.

We have included in this report every patient who received treatment for 12 hours or more. Seven patients are excluded who

* Merck & Co., of Rahway, N. J., kindly supplied the Sulfapyridine used in this study.

† Most of our cases were seen at the following hospitals in and around Philadelphia: Philadelphia General, Hospital of the University of Pennsylvania, Hahnemann, Graduate, Misericordia, Presbyterian, Episcopal, Mt. Sinai, Fitzgerald-Mercy, St. Mary's and Germantown.

died in less than 12 hours after drug therapy was begun. Sulfapyridine therapy was instituted in every patient with penumonia offered to us for study from whom a typable pneumococcus was recovered, regardless of complications or the apparent severity of the infection. Patients who received therapeutic doses of serum either before or after sulfapyridine therapy are not included in this report. Even though we tried to avoid a combination of the two types of therapy, 12 patients were given both serum and sulfapyridine. One death occurred in the group of 5 that had sulfapyridine followed by serum and one in the other group of 7 that received serum first.

TABLE 1.—RESULTS OF SULFAPYRIDINE TREATMENT IN 400 TYPED CASES.

Type.	Negative blood culture.			Positive blood cultures.			Total.		
	No. of cases.	Fatal cases.	Mortality, %.	No. of cases.	Fatal cases.	Mortality, %.	No. of cases.	Fatal cases.	Mortality, %.
I	83	3	3.6	21	3	14.3	104	6	5.8
II	27	1	3.7	3	1	33.3	30	2	6.7
III	63	10	15.9	4	1	25.0	67	11	16.4
IV	20	1	5.0	2	1	50.0	22	2	9.1
V	31	0	..	6	2	33.3	37	2	5.4
VI	13	0	..	0	0	..	13	0	
VII	21	1	4.8	0	0	..	21	1	4.8
VIII	23	0	..	1	0	..	24	0	
IX	4	0	..	0	0	..	4	0	
X	1	0	..	0	0	..	1	0	
XII	8	0	..	0	0	..	8	0	
XIII	1	0	..	0	0	..	1	0	
XIV	17	0	..	1	0	..	18	0	
XV	4	1	25.0	1	0	..	5	1	20.0
XVI	3	0	..	1	1	100.0	4	1	25.0
XVII	2	0	..	0	0	..	2	0	
XVIII	4	0	..	0	0	..	4	0	
XIX	7	0	..	0	0	..	7	0	
XX	2	0	..	0	0	..	2	0	
XXI	1	0	..	0	0	..	1	0	
XXII	2	0	..	0	0	..	2	0	
XXIII	6	0	..	0	0	..	6	0	
XXIV	2	0	..	0	0	..	2	0	
XXV	3	1	33.3	0	0	..	3	1	33.3
XXVII	4	0	..	0	0	..	4	0	
XXVIII	2	1	50.0	0	0	..	2	1	50.0
XXIX	3	0	..	1	0	..	4	0	
XXX	1	0	..	0	0	..	1	0	
XXXI	1	0	..	0	0	..	1	0	
Total . .	359	19	5.3	41	9	22.0	400	28	7.0

Therapeutic Results. The results of the sulfapyridine treatment are given in Table 1; 84% of the cases were caused by the pneumococcus Types I to VIII and Type XIV. In 197 cases, approximately one-half of the entire group, the pneumococcus involved belonged

to one of the first three types. In this group of 197 cases, the mortality was 9.6%. There were 104 cases of Type I infection with a mortality of 5.8% and 63 cases of Type III infection with a mortality of 16.4%. The mortality rate of Type III is generally high, due we believe to the fact that the Type III organism is often the cause of pneumonia in debilitated or senile patients. This is suggested by the average age of 54.6 years in the group of 11 fatal cases of

TABLE 2.—ANALYSIS OF FATAL CASES IN TYPED SERIES.

Number.	Age, years.	Day of disease treatment began.	Type.	Total dosage, gm.	Remarks.
1	44	6	I	8	Moribund on admission
2	43	8	I	50	Developed empyema and meningitis
3	63	5	I	8	Moribund on admission
4	56	3	I	8	Moribund on admission
5	58	3	I	21	Cardiac decompensation
6	55	1	I	30	Temp. nor.; died of coronary occlusion
7	73	1	II	24	
8	57	3	II	12	Moribund on admission
9	35	7	III	6	Moribund on admission
10	75	3	III	32	
11	51	5	III	10	Moribund on admission
12	65	4	III	5	Moribund on admission
13	66	2	III	35	
14	58	14	III	25	Severe alcoholic
15	47	14	III	20	Pneumonia complicating subac. bact. endocarditis
16	57	10	III	25	Uremic on admission
17	68	6	III	19	Cardiac decompensation
18	79	3	III	25	Chr. card. decomp.
19	45	7	III	19	Moribund on admission
20	62	5	IV	11	Moribund on admission
21	70	6	IV	9	Card. decomp. on adm.
22	57	8	V	10	
23	12	4	VII	20	Clinically well. Died in epileptic convulsion
24	32	5	VII	102	Developed empyema and meningitis
25	57	4	XV	25	Cardiac decompensation
26	37	3	XVI	5	Paretic. Moribund on admission
27	68	2	XXV	35	
28	37	7	XXVIII	25	Temp. nor. Diabetic. Died in insulin shock

Type III infection. The incidence of bacteremia in this series was low. In only 41 patients was a positive blood culture obtained, with a mortality in this group of 22%. An analysis of all the fatal cases is presented in Table 2. Every patient receiving treatment for more than 12 hours who died during the period of hospitalization has been counted as a death from pneumonia. This has resulted in the inclusion of 4 cases as deaths in which the patients had fully recovered from the pulmonary infection. Case VI died on the fifth

day of convalescence of coronary occlusion; Case XXIII died in a epileptic convulsion just before discharge; Case XXV, a chronic cardiac died after 10 days of normal temperature in a sudden attack of decompensation; Case XXVIII died in a hypoglycemic reaction following insulin on the fifth day of normal temperature. The mortality in both the white males and females was higher than in either sex in the negro (Table 3). The incidence and mortality according to age are given in Table 4. In Table 5 we have attempted to show the influence of pre-existing disease or complicating conditions on mortality. In those pneumonia patients who had had pre-existing nephritis or cardiac disease the mortality (23.7%) was approximately 3 to 4 times the mean mortality for the typed group as a whole.

TABLE 3.—INCIDENCE AND MORTALITY ACCORDING TO RACE AND SEX IN TYPED SERIES.

Race.	Sex.	No. of cases.	Incidence, %.	No. of deaths.	Mortality, %.
White	Male	190	47.5	15	8.0
	Female	113	28.3	9	7.9
Negro	Male	63	15.7	3	4.8
	Female	34	8.5	1	2.9

TABLE 4.—INCIDENCE AND MORTALITY AMONG AGE GROUPS IN TYPED SERIES.

Age groups.	No. of cases.	Incidence, %.	No. of deaths.	Mortality, %.
12 to 19	45	11.2	1	2.2
20 to 29	71	17.8	0	
30 to 39	74	18.5	4	5.4
40 to 49	86	21.5	4	4.7
50 to 59	59	14.8	9	15.3
60 to 69	42	10.5	6	14.3
70 and over	23	5.8	4	17.4

TABLE 5.—INFLUENCE OF OTHER DISEASES ON MORTALITY IN TYPED CASES.

Disease.	No. of cases.	Fatal cases.	Mortality, %.
Heart disease	28	7	25.0
Syphilis	20	1	5.0
Diabetes	15	1	6.7
Postoperative	13	0	
Nephritis	10	2	20.0
Alcoholism	8	1	12.5
Asthma	8	0	
Pregnancy	8	0	
Cirrhosis	2	0	

Dosage. The majority of the patients were treated according to the dose schedule recommended by Evans and Gaisford.[6] An initial dose, by mouth, of 2 gm. was followed by .1 gm. every 4 hours until a total of 25 gm. had been given. Our experience has led us to modify the total dosage in certain respects. Though patients treated during the first 5 days of their disease received, as a rule, a total of 25 gm., when therapy was begun more than 5 days after the onset, a total of 15 gm. was usually sufficient to con-

trol the infection. Every patient with a positive blood culture received at least 25 gm.; in a few instances a total of 50 gm. was given. Whenever there was evidence of spread of the infection, even though the temperature had dropped to normal, larger total amounts were administered. The level of sulfapyridine in the blood was estimated at least once during the course of treatment in the majority of the patients. As stated in our former paper,[8] we have not been able to correlate concentration of the drug in the blood with either the dose or the clinical result. The average level of sulfapyridine in the blood was between 4 and 6 mg. per 100 cc. (range from 1.2 to 18 mg.).

In elderly patients and especially those with renal involvement the total dosage rarely exceeded 15 gm. The possibility that in this group there was impaired elimination of the drug was suggested by a high level of sulfapyridine in the blood of several patients after relatively small doses of the drug. On the other hand, one patient, who developed a typical Type V pneumococcic pneumonia during an acute nephritis, had a low level of sulfapyridine in the blood after 7 gm. of the drug had been given within 24 hours.

This man, aged 47, had had gross hematuria, a cloud of albumin, and a low fixed specific gravity for 2 weeks before developing pneumonia. He was given the routine treatment of sulfapyridine, consisting of an initial dose of 2 gm. followed by 1 gm. every 4 hours. After 6 doses, or a total of 7 gm. had been given without the development of vomiting, his blood level of sulfapyridine was only 3.8 mg. per 100 cc. of blood. On the same day the level of urea nitrogen in his blood was 120 mg. per 100 cc. of blood. In spite of this low level of sulfapyridine in the blood and the azotemia, there was a critical fall in temperature on the day after treatment was started. It is of interest that with recovery from the pneumonia, there was rapid improvement in the nephritis, so that after 5 days of sulfapyridine therapy repeated urinalyses showed no red blood cells and only a faint trace of albumin. The level of blood urea nitrogen improved steadily to be 29 mg. per 100 cc. 17 days after the course of sulfapyridine was started.

The question of renal damage by sulfapyridine is becoming increasingly more important. Stockinger[20] first reported finding sulfapyridine crystals in the urine of treated patients. Antopol and Robinson[4] and Gross, Cooper and Lewis[10a,b] have found urinary concretions composed mainly of free and acetylated sulfapyridine in rats, rabbits and monkeys given sulfapyridine orally. More recently, Southworth and Cooke[19] have reported hematuria, abdominal pain and nitrogen retention in 3 patients who had been given sulfapyridine by mouth.

Our data were analyzed with a view to discovering renal damage. Of 381 patients who had urinalyses during the acute stage of the disease, red blood cells were found in the urine of 27 cases, a hematuria incidence of 7%. As Reimann[17a] states that casts and red blood cells are found in about 4% of lobar pneumonia cases, it would appear that hematuria was significantly increased in our

patients after sulfapyridine therapy. In only 14 of 277 patients who had urinalyses during treatment, however, was hematuria discovered after the initiation of sulfapyridine therapy. This incidence of 5.4% is but little above Reimann's hematuria incidence.

In most cases hematuria was observed in but one or two specimens and often disappeared even though sulfapyridine medication was continued. The following case is representative of this group.

A male, aged 18, with a Type V pneumonia, was treated on the third day of his disease with sulfapyridine. On the fifth day, the urine was found to contain many red cells and abundant albumin. A careful search of the sediment did not reveal any crystals of the drug. On the next day, the red cells were less numerous, and on the seventh day despite the fact that the sulfapyridine medication had not been stopped, the urine was clear. There was no increase in the blood urea nitrogen and during convalescence a urea clearance of 120% of average normal function was reported. Dr. Eugene Landis in consultation believed that in this patient the hematuria and albuminuria were due, not to the sulfapyridine but to a focal nephritis such as may occur in an acute febrile illness.

In a further attempt to discover any harmful effect of sulfapyridine therapy on the kidney, sections of kidneys from 12 fatal cases were examined by Dr. Herbert Fox. He observed no consistent change from normal that could not be explained by an acute febrile illness.

In spite of our failure to demonstrate renal damage, the high incidence of hematuria, which in 3 cases was gross, and the laboratory and clinical experience of others leads us to believe that renal damage during sulfapyridine treatment may be regarded in the future as one of the more common sequelæ of this type of drug therapy.

At this time we cannot state definitely what constitutes adequate dosage. It is well recognized from comparisons of dosage and blood concentration that there is a wide variation in the rate of absorption in different patients, and in the same patient from day to day. It is quite probable that establishment of optimum blood concentration of the drug must await more soluble derivatives of sulfapyridine, and more extensive studies on the acetylated and non-acetylated drug. At present, we are not in a position to state what constitutes the optimum blood level of the drug. The fact that we have observed excellent clinical improvement in patients whose blood level did not exceed 2.0 mg. per 100 cc. indicates the limitations of simple blood level determinations.

Influence of the Drug on the Course of the Disease. The most striking clinical observation was the frequency and rapidity of the drop in temperature after the drug treatment was started. This drop in temperature, which usually occurred within 24 to 36 hours, was in most instances followed closely by definite improvement in the toxemia and general well-being of the patient. The critical

termination of the febrile course after therapy was begun, even in the first few days of the disease, was very dramatic as can be seen in Charts 1 and 2.

Whether or not resolution of the pneumonic consolidation is hastened by the action of the drug, we have been unable to determine. The fact that physical signs often persisted for some days after the temperature had become normal, the toxemia had disap-

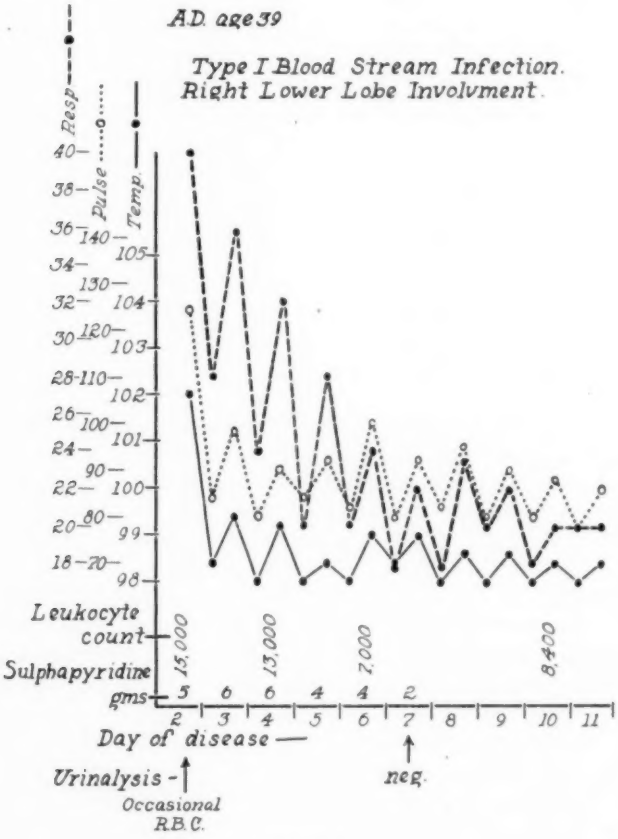

CHART 1.

peared, and the general well-being of the patient had returned to normal, strongly suggests that once red hepatization has occurred the pathologic changes in the lung must undergo their usual process of resolution even though bacterial invasion is no longer a problem. In a few patients, however, who gave a typical history of the onset of pneumococcic pneumonia (chill, bloody sputum and chest pain), therapy was started before true pulmonary consolidation could

be demonstrated by either physical or Roentgen examination. In these cases, followed by frequent Roentgen and physical examinations, dense consolidation seemed to be aborted and resolution of the process to occur more readily.

The relationship between the day of disease on which therapy was started and the drop in temperature is given in Chart 3. In the majority of patients the temperature fell by crisis. In some, a low grade fever persisted for several days after the critical drop; in

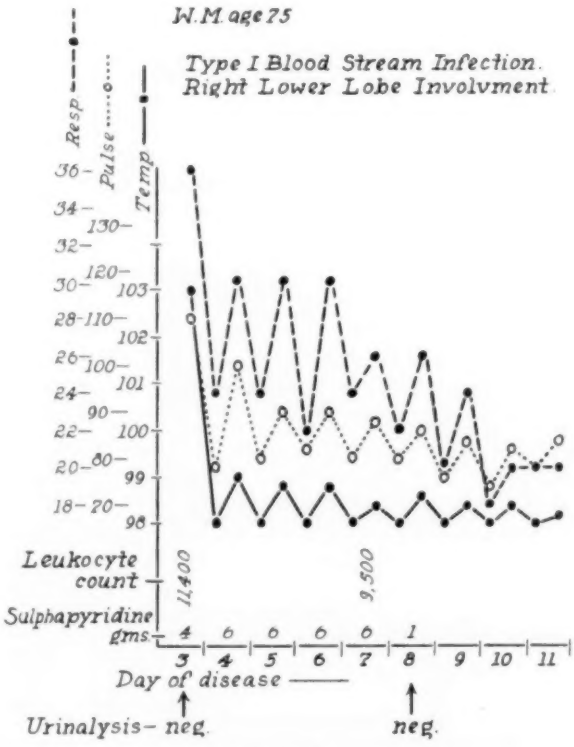

CHART 2.

such cases careful evaluation of the individual factors was required before outlining further therapy. Blood counts and urinalyses were obtained as frequently as possible within reason during the course of treatment and convalescent period. Even though the cases were followed personally by one of the authors, the fact that they were drawn from more than 15 hospitals, including a large municipal hospital, made regular studies almost impossible. In most patients, the critical drop in temperature was followed within 12 to 24 hours by a rapid fall toward normal of the total white blood count. This,

we believe, represents a favorable sign, because in cases in which the leukocyte count remained elevated, despite what was thought to be adequate drug therapy, the usual clinical improvement was retarded.

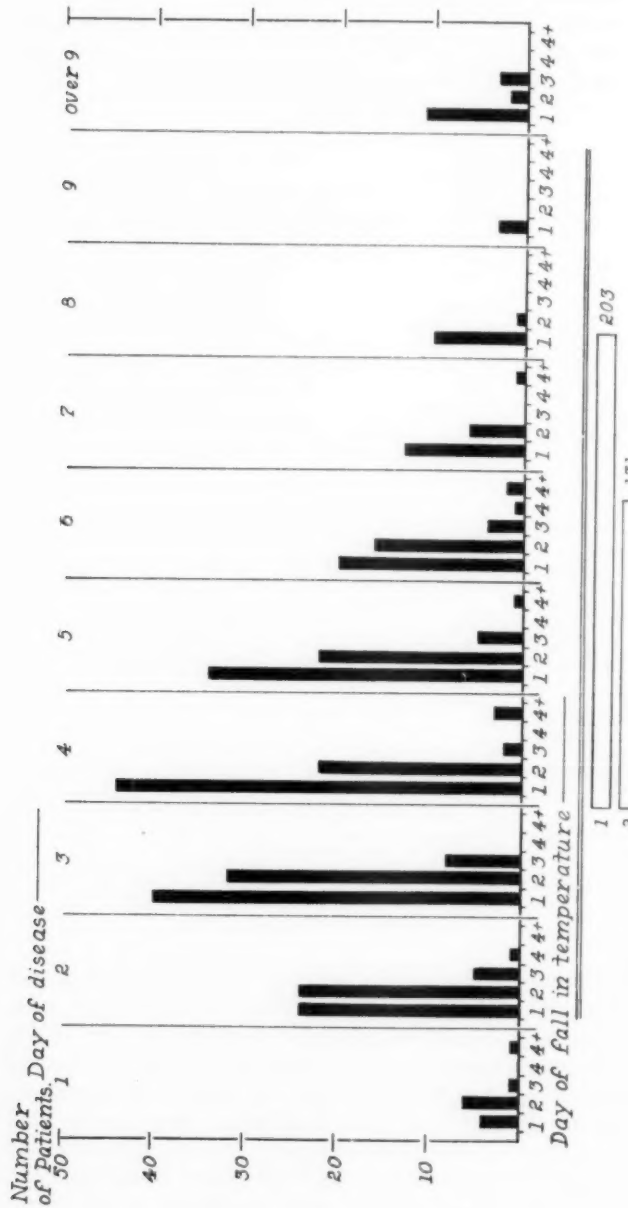

CHART 3.—Time of critical drop of temperature following initiation of sulfapyridine therapy in relation to day of disease.

In those cases that developed a spread of the infection or other complication, such as empyema, meningitis, or drug reaction, we often encountered marked elevation in the total white count several days after treatment had been started.

TABLE 6.—INCIDENCE OF COMPLICATIONS IN TYPED SERIES.

Complication.	Number.	Incidence, %.
Massive effusion	11	2.8
Empyema	5	1.3
Phlebitis	3	0.8
Otitis media	2	0.5
Meningitis	2	0.5
Total	23	5.9

Complications (Table 6). There were only 5 cases in which frank empyema developed. In 11 others that developed large pleural effusions, thoracentesis was performed for diagnostic purposes or because of mechanical difficulties with respiration. Most authorities agree that a small amount of pleural fluid usually develops in pneumococcal pneumonia. The incidence of empyema is known to vary from one series of pneumonia cases to another, depending upon the virulence and specific type of the pneumococcus. It is generally agreed that the incidence of empyema in patients with Type I pneumonia is consistently high, according to Reimann[17b] about 13%. In our 104 cases of Type I pneumonia, there were only 2 cases of empyema. As noted in Table 2, there were only 2 fatalities in the group having complications, Patients II and IV both having empyema and meningitis. This low incidence of septic complications substantiates our belief in the ability of the sulphanilamide group of drugs to prevent the spread of an infectious process through normal tissue.

TABLE 7.—TOXIC REACTIONS IN TYPED SERIES.

Toxic reactions.	Number.	Incidence, %.
Nausea	212	53.0
Vomiting—troublesome	144	36.0
severe	23	5.8
Dermatitis	2	0.5
Acute hemolytic anemia	1	0.25
Leukopenia	2	0.5
Drug fever	2	0.5
Psychosis	4	1.0

Toxic Reactions (Table 7). The most troublesome and frequent untoward effects of the drug were nausea and vomiting. Both appeared, as a rule, during the first 24 hours of treatment; and we agree with Marshall[14] that these are probably of central rather than local origin, as both have been observed following the administration of the soluble salt of sulfapyridine intravenously. In 25 patients the vomiting was so severe that drug therapy was stopped; but in no

case was this done before 12 gm. had been administered. None of these patients died. In 144 patients, the vomiting was a source of distress to the patient, but not sufficiently severe to require total cessation of the therapy. That vomiting did not necessarily hinder absorption of the drug was shown by several patients with high blood sulfapyridine levels in whom vomiting had occurred shortly after the administration of each dose. In these patients we felt that it was due to a psychic reaction caused by the unpleasant taste of the drug. No correlation was observed between the level of sulphapyridine in the blood and the development of nausea and vomiting. The following measures were adopted, all of which appeared to improve the tolerance for the drug: 1, Mixing the drug with water, fruit juices or milk; 2, administration of small amounts of sodium bicarbonate or aluminum hydroxide solution after ingestion of the drug; 3, temporary omission of treatment for 1 or 2 doses; 4, the use of barbiturates and chloral hydrate; 5, the introduction of sodium chloride and dextrose intravenously; 6, the use of nicotinic acid in daily doses of 300 to 450 mg.

Item 5 appeared to be a valuable method of lessening the severity of the nausea and vomiting as well as providing for the restoration of a normal fluid and electrolyte balance. This assumes even greater importance in the dehydrated patient in view of the recent reports of renal damage.

Nicotinic acid has been tried by us recently because McGinty, Lewis and Holtzclaw[13] have reported that sulphanilamide reactions were relieved by nicotinic acid; it has given us encouraging results in a few patients.

The toxic reactions shown in Table 7 are similar to those associated with sulphanilamide treatment; in our experience they do not occur as frequently with sulfapyridine as with sulphanilamide. Marked leukopenia developed in 2 instances but no instance of agranulocytosis was observed. Acute hemolytic anemia occurred in only 1 patient, but in several others there was a drop in the red blood count of over 2 million and a reduction in hemoglobin up to 40%. In patients who were markedly dehydrated at the time of the first blood count and who then received adequate fluid and sulfapyridine, it is obviously difficult to evaluate the lower counts which followed. Cyanosis is likewise difficult to evaluate in a disease involving the lungs. In about 12% of our cases it was found either to have appeared or to have increased in intensity after initiation of the sulfapyridine therapy. From our experience with the cyanosis associated with sulphanilamide therapy, and aware of the work of Marshall and Walzl,[15] who observed that clinical cyanosis following sulphanilamide therapy did not necessarily involve a decrease in the oxygen carrying capacity of the red blood cells, we have not felt that cyanosis following sulfapyridine therapy was an indication for withdrawal of the drug.

In only 2 patients was a diagnosis of drug fever made; this leads us to feel that we might have overlooked this type of reaction in certain cases. In not a few patients there was noted a secondary rise in the temperature following the critical fall; this we ascribed to various causes and often increased the dose of sulfapyridine. In a study of gonorrheal urethritis treated with sulfapyridine[12] a febrile reaction was observed in 7 of 80 patients, unassociated with a flare-up of the disease process. As febrile episodes in this condition are usually associated with obvious extension of the infection, it seemed highly likely that the percentage of febrile reactions to sulfapyridine was much higher than that indicated by the 2 cases recognized in the pneumonia cases. It is true, of course, that while lower doses were given to the group with gonorrheal urethritis, the patients were ambulatory and were treated for longer periods of time.

As sulfapyridine occasionally produces untoward effects, it should be used with full recognition of its toxic possibilities. It is important to follow closely the patients to whom it is being administered. The urine should be studied repeatedly for red blood cells, crystals and urobilin, and the blood picture for anemia and neutropenia. Any secondary rise in temperature must be carefully analyzed in view of the possibility of drug fever. Even greater importance than usual must be laid to the avoidance of dehydration for fear of allowing sufficient concentration of the urine to cause crystallization and development of sulfapyridine concretions within the urinary tract. Plasma chloride studies are indicated in those patients with severe vomiting and blood urea nitrogen determinations in patients in whom renal injury is suspected.

TABLE 8.—INCIDENCE AND MORTALITY AMONG AGE GROUPS IN NON-TYPED SERIES.

Age groups, yrs.	No. of cases.	No. of deaths.	Mortality, %.
12 to 19	19	0	0.0
20 to 29	18	1	5.6
30 to 39	12	0	0.0
40 to 49	20	2	10.0
50 to 59	15	1	6.7
60 to 69	12	2	16.7
70 and over	4	3	75.0
Total	100	10	10.0

Non-typed Cases (Table 8). We have also analyzed our first hundred records of pneumonia patients from whom no typable pneumococcus could be isolated. It is to be noted that these cases are not consecutive and, of course, do not necessarily fall into one group. Most of them represent patients in whom the severity of the infection warranted immediate treatment, and sulfapyridine therapy was instituted with the expectation that a specific pneumococcus would be isolated from the sputum or blood culture. In 35 cases a pneumococcus was recovered that could not be typed; in 15

the blood culture was negative and no sputum was obtained; and in the remaining 50 there was either a mixture of organisms or the predominant organism was not a pneumococcus. Blood cultures, taken in 66% of these cases, were positive in 3. In 2 of these an untypable pneumococcus was recovered and the third yielded a hemolytic streptococcus. One of the 2 patients with blood stream invasion by untypable pneumococci died, the other developed empyema but eventually recovered. The patient with streptococcus infection made an uneventful recovery.

Evaluation of the effectiveness of sulfapyridine therapy in this heterogenous group of cases is difficult. In some the drug had little or no effect. This was especially true in the staphylococcus cases and in those with atypical onset, relative bradycardia, and normal leukocyte count. In most of these patients who had typical findings of lobar pneumonia, the drug seemed as effective as in the typed cases. The complications and toxic effects encountered in the non-typed cases were comparable to those described in the typed series. Of 66 patients that had urinalyses during the period of treatment with sulfapyridine, only 3 patients showed (microscopic) hematuria.

Comment. In view of our experience thus far, sulfapyridine appears to be an effective therapeutic agent in the treatment of pneumococcic pneumonia. That the apparent success of the drug in the treatment of our patients has been influenced by a possible reduction in the virulence of the pneumococcus this year must be considered. Experience has shown that the virulence of the higher numbered types of pneumococci varies from year to year, while that of the first three types and especially Type I remains fairly constant. Our mortality rate was favorable (in the first 3 types: Type I, 5.8%, Type II, 6.8%; Type III, 16.4%). The high mortality of the Type III cases was, we believe, due to the fact that this organism selects the debilitated and aged patient. Our mortality in Type I compares favorably with the mortality of 5% in 60 other cases reported in the literature,[1,3,5,9,11,16,18,20] and is, we believe, significant.

We have suggested certain potentially fatal reactions that might occur with the use of sulfapyridine. In our 500 cases, however, there was not one death that we believe was caused by this drug. It was equally efficacious in pneumonias due to the various types of pneumococci and in those cases in which the predominant organism was an untypable pneumococcus. This type of therapy can be instituted as soon as a diagnosis of pneumonia is made and need not wait as in specific serum therapy for the production of sputum and the typing of the organism. No patients were encountered who could not tolerate a therapeutic dose of the drug, whereas 4 of our patients had been unable to take serum because of serum sensitivity. One of them went into syncope and almost died after a small test dose of horse antiserum. Undoubtedly

had all the cases been tested for horse serum sensitivity other sensitive cases would have been discovered.

Summary. 1. A mortality of 7% is reported in a series of 400 patients with typed pneumococcic pneumonia treated with sulfapyridine.

2. Of these 400 cases, 197 were caused by the first three types of pneumococci, with a mortality of 5.8% in 104 cases of Type I pneumonia, 6.7% in 30 cases of Type II pneumonia, and 16.4% in 67 cases of Type III pneumonia.

3. Our experiences regarding dosage, influence of the drug on the course of the disease, complications and toxicity are described.

4. One hundred cases of non-typed pneumonia treated with sulfapyridine are briefly discussed.

This large series of cases was only made possible through the generosity and cooperation of a number of physicians in and around Philadelphia. The authors wish to express their appreciation to these men, to Miss Helen Lynch and to Dr. J. H. Clark for their technical assistance, and to Dr. I. S. Ravdin for his constant interest and helpful suggestions.

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THE USE OF SULPHANILAMIDE IN ACUTE SUPPURATIVE ARTHRITIS DUE TO THE HEMOLYTIC STREPTOCOCCUS.

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Observations made during the course of the patient's illness, which are recorded in the following case report, emphasize the value of sulphanilamide in controlling a severe type of hemolytic streptococcic sepsis. Following an attack of acute tonsillitis, the patient

developed acute glomerular nephritis with a severe degree of nitrogen retention, pneumonia, and suppurative arthritis of the knee. Sulphanilamide was administered to the patient, and a complete restoration of joint function was obtained 5 weeks after entry to the hospital. Simultaneous free sulphanilamide determinations were done on the blood and synovial fluid. During the same period, all signs of nephritis disappeared. Of considerable importance were the results of studies of stained smears of the synovial exudate with particular reference to the morphologic changes in the streptococcus. These latter observations confirmed *in vitro* studies made by others[1,2] on the mode of action of sulphanilamide.

Case Report. J. L., a 35-year-old, white male laborer, was in good health until the sudden onset of tonsillitis. His temperature was 104° F., but his condition gradually improved, and within a few days he was up and out of doors. Two weeks after the onset, he suffered from a chill lasting 30 minutes. He attempted to keep on working but 2 days later he "ached all over," had fever, and developed a cough. A diagnosis of pneumonia was made and confirmed roentgenologically. He was confined to bed, and his left knee became swollen and painful and the urine became scanty and bloody.

He had had scarlet fever, measles, mumps, and pertussis in childhood.

On entry to the hospital, the patient appeared acutely ill and stuporous. There was an urinferous odor to his breath. The fundi appeared normal. His pharynx was reddened, but no exudate was present. The neck veins were distended. His heart was slightly enlarged to the left by percussion. There was a systolic murmur along the left sternal border. No diastolic murmur was heard. The rhythm was regular. The blood pressure was 122/74. The venous pressure in the antecubital vein of the right arm was 4.5 cm. of blood. No abnormal findings were apparent in the lungs. The abdomen was soft, and no masses were palpated. There was no edema of the extremities. The left knee, which was fixed in semiflexion, had periarticular swelling, increased temperature of the skin, and marked tenderness on motion and palpation. There was evidence of a marked effusion into the synovial cavity.

Roentgenologic examination of his chest revealed a density in the right upper lobe, which was designated as characteristic of an infarct. Two weeks later another examination showed a normal lung field. A roentgenogram of his left knee was interpreted as showing minimal lesions involving the articular surfaces. Two electrocardiograms were interpreted as being within normal limits.

Repeated urine analyses showed a specific gravity ranging between 1.007 and 1.018. Albuminuria was present for the first 3 weeks. The sediment contained many erythrocytes and leukocytes, both of which gradually decreased in number until the time of his discharge, when only an occasional cell of each type was present. His hemoglobin was 71% on entry (Sahli), erythrocytes 5,050,000 per c.mm., and white blood cells 14,700. He developed a progressive anemia, so that 3 weeks after entry his hemoglobin was 48%, with 2,950,000 erythrocytes per c.mm. The white blood cells level rose to 32,600 per c.mm. while he was receiving sulphanilamide. His blood urea nitrogen level is charted in Figure 1. During the first week in the hospital it was 81 and 104 mg. %. The creatinine was 2.4 mg. % and the uric acid 6.4 mg. His total plasma proteins were 6.3 gm., with 3.4 gm. of albumen and 2.8 gm. of globulin. The carbon dioxide combining power of his blood serum was normal. The sedimentation rate of his

erythrocytes during his first week in the hospital was 111 mm. during the first hour, and 127 mm. during the second (Westergram).

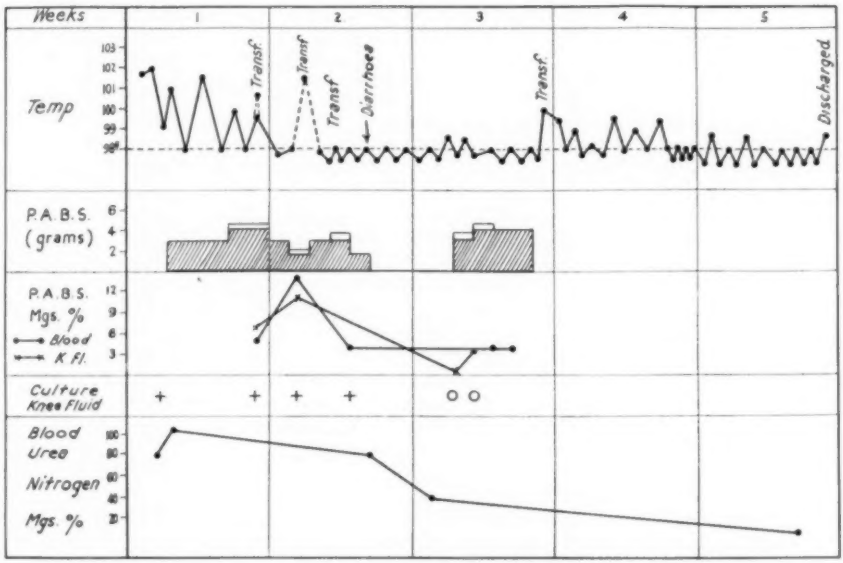

FIG. 1.—The course of a patient treated with sulphanilamide, who had a suppurative arthritis of the knee and acute glomerular nephritis.

TABLE 1.—CHARACTERISTICS OF ASPIRATED SYNOVIAL FLUID.

Date of aspiration, 1938.	Amt. in cc.	Appearance.	Culture.	Gram stain of fluid.
9–3	60	Green, thick, purulent	B. hemolytic streptococcus	Most of cells are neutrophils with occasional clasmatocyte. Short chains of Gram-positive cocci, mostly *extracellular*. Very few within cells.
9–7*	80	Thick, purulent with small masses of fibrin	B. hemolytic streptococcus	Neutrophils again predominate. Most of cocci now *intracellular*, filling the cytoplasm of the leukocytes. Cocci remaining extracellular, stain poorly (part of chain Gram-neg.); large swollen pleomorphic cocci; "Indian club" forms.
9–9*	40	Bloody, purulent	B. hemolytic streptococcus	Some type of cell predominating. Very few cocci seen—all *intracellular* and none extracellular.
9–12*	15	Thin, cloudy	B. hemolytic streptococcus	No organisms seen.
9–16*	40	Purulent, thick	Sterile	No organisms seen.
9–17*	25	Thin, sero-purulent	Sterile	No organisms seen.
9–26	10	Sero-purulent	Sterile	No organisms seen.

* Following aspiration 20 cc. of 0.8% sulphanilamide in physiologic saline solution introduced into joint cavity. Drug also given orally.

The patient was under observation in the hospital for 5 weeks. Two days after entry, 60 cc. of green, thick, purulent material were aspirated from the synovial cavity of the left knee. A pure culture of a beta hemolytic

streptococcus was isolated from the fluid. The morphologic features of the fluid stained by Gram's method were studied microscopically (findings tabulated in Table 1). It should be pointed out that examination of the fluid obtained at the initial aspiration showed short chains of cocci which were extracellular. Only an occasional coccus was found within the cytoplasm of the phagocytes. Shortly after sulphanilamide therapy was instituted, the synovial fluid was examined again. At this time the cytoplasm of many neutrophils and clasmatocytes were filled with cocci. Many of the extracellular organisms showed pleomorphic changes and stained poorly. Following the initial aspiration, the patient was considerably relieved. Because of his renal failure, sulphanilamide was given cautiously. Three days after entry, he was given a total of 40 grains a day in divided doses, for 3 days. He was then given 60 grains a day. After 3 days the free sulphanilamide present in his synovial fluid was 6.3 mg. %, and in the blood 5.1 mg. Two days later the levels were 10.8 mg. % in the synovial fluid, and 12.4 mg. in the blood. Other determinations are recorded in Figure 1. The patient was also given 4 transfusions with citrated blood because of his anemia. After his first week in the hospital his temperature became normal. During the second week of sulphanilamide therapy, he developed a diarrhea. It was difficult to ascertain whether this was due to his uremia or to the sulphanilamide. The drug was omitted for several days, his diarrhea subsided, and then sulphanilamide was again administered. There was no recurrence of this diarrhea.

The patient improved considerably as to his general condition. The pain in the joint gradually subsided. Aspiration of the synovial cavity yielded sterile fluid on 2 occasions during the third week. The sulphanilamide was discontinued. He was allowed out of bed 5 weeks after entry to the hospital. He had no pain in the knee joint. At this time, there was no nitrogen retention. Roentgenologic examination showed no change in the articular surfaces. He was able to extend the leg fully, and there were 10 to 15 degrees of flexure deformity. There was some periarticular swelling and definite atrophy of the quadriceps muscle. It should be stated that at no time did he have an elevation of his blood pressure over the normal limits.

The patient was seen 4 weeks after he left the hospital. He had gained weight and he had no pain in his knee joint. Some periarticular swelling, and atrophy of the quadriceps were still present, but he was able to flex and extend completely the left lower leg. His blood urea nitrogen was normal. Urine analysis revealed no albuminuria, and the sediment contained 2 to 3 red blood cells and an equal number of leukocytes per high power field. Three weeks later, he informed us that he had returned to work.

Discussion. Suppurative arthritis due to the hemolytic streptococcus is marked by its chronicity and the destruction of joint tissue. Even when the nature of the joint changes is recognized early, and surgical drainage is instituted, recovery is usually accompanied by ankylosis. In the present case, there was a complete restoration of joint function, which we attribute to the result of sulphanilamide therapy. Prior to administering the drug, the organisms in the synovial exudate were extracellular, but after its exhibition, the bacteria were intracellular, and many of those remaining extracellular showed degenerative changes. We have never seen such an abrupt change in the position, morphology, and staining characteristics of the hemolytic streptococcus in examinations of many synovial exudates from patients not treated with sulphanilamide.

The drug was given orally and injected in solution directly into the joint cavity. Whether the latter procedure is necessary, only further experience will decide. It would appear that the free sulphanilamide level of the synovial fluid approximates that of the blood level. We have also made a similar study of the pleural exudate of a patient with a hemolytic streptococcic empyema. The same changes were observed in the stained smears before and after sulphanilamide therapy.

Gay and Clark[1] studied the mode of action of sulphanilamide by exposing hemolytic streptococci to rabbit serum containing the drug. After a period of time, stained preparations of the mixture showed the organisms to have distinct degenerative changes. The chains were markedly elongated, and the individual cocci were swollen, metachromatic, and pleomorphic. However, the distorted cells were still encapsulated, and had not lost their virulence permanently. Lockwood[2] in another study made similar observations. When organisms were added to sulphanilamide and serum, the first change noted in the organism was the persistence for from 8 to 12 hours of a pink capsule. The capsule normally persists for only 4 hours. At the same time, there was an increase in the size of the cocci and a tendency toward the formation of longer chains. Then there appeared irregularities in the contour of the chains, coalescence of cocci, marked pleomorphism, and transparent gaps in the chains. The study of Gram-stained smears of the exudate from the joint cavity in the present case revealed similar degenerative changes These *in vivo* observations confirm the *in vitro* studies of the foregoing investigators.

It would appear that from the foregoing observations, and those of others[3] that sulphanilamide is an effective therapeutic agent in the treatment of suppurative arthritis due to the hemolytic streptococcus.

Summary and Conclusions. 1. A patient with severe streptococcic sepsis, including tonsillitis, pneumonia, acute glomerular nephritis with nitrogen retention and suppurative arthritis of a knee joint, was treated with sulphanilamide. There was complete restoration of joint function.

2. A study of the exudate from the joint cavity obtained before sulphanilamide therapy showed short chains of cocci, mostly *extracellular*. After sulphanilamide had been administered, large numbers of cocci were *intracellular*, and the extracellular organisms were pleomorphic, and stained poorly. These observations confirm the experimental studies of others.

3. The free sulphanilamide level of synovial fluid tends to approximate the level in the blood.

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A NOTE ON THE OCULAR SYMPTOMS OCCURRING FROM MALNUTRITION IN HUMAN BEINGS.*

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Recently we have described spectacular improvement in a large series of persons with pellagra, beriberi, and riboflavin deficiency following the administration of synthetic nicotinic acid, synthetic thiamin hydrochloride, and synthetic riboflavin.[2] After the initial improvement, the addition of these synthetic chemical substances as daily supplements to the inadequate diets of these persons is beneficial in that many of them become strong enough to work, with the result that they often buy a better diet and subsequently are restored to good health. Those whose diet remains the same have better health with these supplements than without them; nevertheless, they often remain undernourished and in ill health. This suggests that even though three essential substances, nicotinic acid, thiamin hydrochloride, and riboflavin, are supplied, the diet usually ingested by these patients must be deficient in still another substance or substances. Past experience has shown that by administering still larger amounts of nicotinic acid, thiamin hydrochloride, or riboflavin, another period of improvement could be induced,[3] but we decided to keep the intake of food and of these synthetic chemical substances constant.

The present report is concerned with 50 patients treated as described above, but who had or developed ocular manifestations, characterized by severe burning, itching, and excessive dryness of the eyes. Oftentimes, the patients describe a "scum" over their eyes and state that the eyes hurt when they go into sunlight. There is granulation and extreme redness of the conjunctiva, particularly of the lower lids, and a striking degree of photophobia. The whole symptom complex is extremely variable from patient to patient and, as a rule, disappears in the late summer and returns again in the early spring. These lesions appear, irrespective of whether the deficiency developed as the result of an inadequate food intake due to economic factors or to chronic alcoholic addiction, or as the result of organic diseases which interfered with adequate nutrition.

Unpublished observations[1] on 70 unselected cases in the nutrition clinic, 20 of whom were children, showed a striking deficiency of vitamin A in the diets of 65 cases. Following the daily administra-

* This study was aided by grants to the University of Cincinnati College of Medicine from the Rockefeller Foundation, the John and Mary R. Markle Foundation, and the Martha Leland Sherwin Memorial Fund.

tion of vitamin A, in the form of carotene in oil* or as oleum percomorphum,† in amounts ranging from 10,000 to 50,000 units, these patients were able to read better, the burning ceased, and the conjunctivitis and photophobia disappeared. Following this therapy there has been, so far, little if any improvement in the dizziness, nystagmus, and dilated pupils, but the patients have reported an increase in strength and feeling of well-being.

The present studies support the hypothesis that dietary deficiency diseases in human beings are nearly always multiple in nature. They show also that certain ocular symptoms, in 50 persons who have had long-continued dietary deprivation, are corrected by the administration of carotene in oil or of oleum percomorphum.

The author is grateful to Miss Jean M. Grant and to Miss Nelwyn Huff for their assistance in this study.

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FAMILIAL POLYCYTHEMIA.

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There are numerous reports on polycythemia since the classical papers of Vaquez and Osler. In most instances, however, descriptions of the disease have limited themselves to individual cases. There is a paucity of well-authenticated reports on the familial and congenital incidence of this disease. This report deals with our findings in 4 cases of polycythemia vera occurring in one family.

Ambard and Fiessinger[1] claim to be the first to call attention to the *congenital* incidence of polycythemia vera. They reported the case of a female who had had cyanosis and dyspnea from birth until the onset of her menstrual life, at which time the symptoms disappeared only to reappear at the menopause. The pertinent data given show that the patient had an erythrocyte count of 7.8 million per c.mm., leukopenia, dilatation of the venous system with such congestion of the viscera that the latter had an "angiomatous" appearance. The spleen was not enlarged. From their autopsy report it would appear that the patient died with hypertensive heart disease with cardiac failure, terminal nephritis and polycythemia. There is no conclusive evidence that the patient had polycythemia early in life.

* Supplied by the S. M. A. Corporation, Chicago, Ill.
† Supplied by Mead Johnson & Co., Evansville, Ind.

In 1908, Nichamin[16] reported a case of polycythemia with splenomegaly and cyanosis. He believed that he was the first to demonstrate the *familial* incidence of the disease for he states that the patient's mother and sister also had enlargement of the spleen and cyanosis. Since he failed to report analytic data on the blood of these relatives, one cannot credit Nichamin with being the first to report the familial incidence of polycythemia vera.

Bernstein[3] was the first to report data on the blood of a patient and the patient's relative. The patient had an erythrocyte count of 12.5 million per c.mm. with 140% hemoglobin; his son had an erythrocyte count of 7.5 million per c.mm. with 120% hemoglobin. The father had splenomegaly and cyanosis; the son's spleen was not palpable. Bernstein's cases are perhaps the first well-established cases of familial polycythemia vera to be found in the literature.

A few years later Tancre[22] reported the findings in a family in which 2 sisters had polycythemia. The patient had an erythrocyte count of 12.6 million per c.mm. with 171% hemoglobin and 17,000 leukocytes; her sister had an erythrocyte count of 6.1 million with 148% hemoglobin. Three other siblings had normal blood pictures.

In 1920, Engelking[8] reported the incidence of polycythemia in 3 generations of one family—the grandmother, the mother and 5 children. The disease was associated with endocrine disturbances, for he found infantilism and menstrual disturbances in the children. He pointed out that the oldest child began to look "blue" at 5 years of age and that the age incidence of the polycythemia—in the 'teens—was well below the usual age incidence 35 to 55 years. A further study on this same family was made by Wieland[25] some 4 years later. At that time, the mother, 3 sons and a daughter showed red cell counts ranging from 8 to 12.16 million per c.mm., hemoglobins ranging from 98 to 150%, hematocrits ranging from 57 to 84% and normal white cell counts. Wieland stated that he believed the disease to be constitutional and hereditary.

In 1922, Doll and Rothschild[7] reported their observation on a family in which the father and 2 children had polycythemia. The father, aged 44, had the following blood findings: erythrocytes, 6.15 million per c.mm.; hemoglobin, 115%; color index, 0.88; leukocytes, 6500 per c.mm.; palpable spleen; blood pressure, 200/115. Five of the 6 children had Huntington's chorea and 2 of these 5 had polycythemia, but the blood findings are very close to the upper limits of normal.

Signorelli[20] reported a clear-cut case of polycythemia in a male but his claim that the patient's sister also has polycythemia is less well established. The cases reported by Curschmann[6] do not have adequate data to show that he was dealing with familial polycythemia.

In 1924, Owen[17] emphasized the familial nature of the disease and

stated that "the disease is a familial one and every case should be investigated from this point of view. There may be other familial defects present also." While Owen's patient undoubtedly had polycythemia the data on the patient's brother are less convincing. Unfortunately, no blood volume studies were made.

Herz[11] reported his studies in 3 families in which he believed there was a familial tendency to polycythemia. He failed to report hematocrit findings, in only 1 case was the hemoglobin over 90%, and only 2 members of the 12 studied had erythrocytes well above normal limits. There is no convincing data that Herz was dealing with familial polycythemia.

Kretschmer,[14] in 1925, reported 3 cases of polycythemia in one family. The children's ages were 5, 7 and 10 years. Only 1 had a barely palpable spleen. The leukocytes were well within normal limits. The onset of symptoms "Krampfe mit Bewusstlosigkeit" and "Blutsturz" occurred as early as the fourth year. There was no hypertension. The red cell counts ranged from 5.7 to 10.2 million per c.mm., and the hemoglobin ranged from 112 to 140%. These cases are clear-cut cases of familial polycythemia.

In 1926, Weil and Stieffel[24] reported the finding of polycythemia in a brother and sister. The brother had splenomegaly while the sister did not.

In 1933, Mussio-Fournier and Lussich-Siri[15] reported the finding of polycythemia in 3 brothers. Their ages were 20, 23 and 27 years and the mother stated that of her 8 children only these 3 had the characteristic wine-colored lips since birth. The red cell counts were not high (5.58, 5.65 and 5.6 million per c.mm.) and only 1 brother had a palpable spleen. The authors stressed the congenital character of familial polycythemia. In the same year, there appeared a splendid report on familial polycythemia by Sporado and Forkner.[21] These authors adequately reviewed the literature and concluded that there were only 6 instances of well-established cases of familial polycythemia reported in the literature, those of Bernstein,[3] Tancre,[22] Engelking,[8] Doll and Rothschild,[7] Kretschmer[14] and Weil and Stieffel.[24] Sporado and Forkner[21] studied a family of 10 over a period of months and concluded that 7 of the members of the family had benign familial polycythemia which they consider differs from polycythemia vera in that in the former there is no leukocytosis, eosinophilia, neutrophilia, increased basal metabolic rate or increased hemoglobin and the disease runs a benign course. They classified their patients into four groups: (*a*) Those with polycythemia with a palpable spleen, 4 cases; (*b*) those with polycythemia without palpable spleen, 3 cases; (*c*) those without polycythemia with a palpable spleen, 1 case; (*d*) those without polycythemia without a palpable spleen, 2 cases—pointing out, and quite correctly, that inability to palpate the spleen does not preclude the presence of splenic enlargement. Unfortunately

Sporado and Forkner failed to report data on the circulating blood volume and figures for circulating cell mass cannot be computed. It should be noted that no case had a hemoglobin above the upper limit of normal and in one-half the cases the mean corpuscular volume was below normal. Unlike Doll and Rothschild,[7] Engelking[8] and Wieland,[25] they found no associated family trait and suggest that the etiology of the disturbance lies in the defect of the germ plasm.

Method. Non-protein nitrogen and sugar were determined by the method of Folin,[9] serum calcium by the Clarke-Collip modification of the Kramer-Tisdall method,[5] serum protein by the micro-Kjeldahl modification of Howe's method.[12] Circulating blood and plasma volume were determined by the method of Rowntree, Brown and Roth.[19] Hemoglobin estimations were done by the Sahli method and checked by the oxygen capacity method of Van Slyke.[23]

The data reported here were obtained on 11 members of a family of 13—2 siblings were not available for examination. The mother stated that of her 11 children, only 4 (Cases 1 to 4) had "red faces" from the time of birth. None of the children had any significant disease in their past histories. There was no evidence of factors which might initiate a secondary polycythemia—physical examination, Roentgen ray studies and spectroscopic examination of the blood failed to reveal congenital heart disease, extensive pulmonary lesions or the presence of abnormal blood pigments. The environmental factors were similar for all members of the family.

TABLE 1.—CLINICAL DATA ON THE 4 CASES.

Case No.	Age, yrs.	Sex.	Blood pressure.	BMR.	Blood Wass.	Spleen.	Remarks.
1	11	F	110/70	−5	Neg.	? palpable	Good health, ruddy face and hands; suffused mucous membranes.
2	13	F	100/80	−18	Neg.	Not palpated	Little's disease; small in stature; ruddy complexion.
3	16	M	125/80	−15	Neg.	Not palpated	Robust; reddened mucous membranes.
4	18	F	118/75	−12	Neg.	Not palpated	Apprehensive; slightly suffused mucous membranes.

Table 1 summarizes some of the observations on the cases with polycythemia. There was no evidence of hypertension; the blood Wassermann reaction was negative in all cases; the spleen was barely palpable in only 1 case; the metabolic rate was normal in Case 1 and below normal in the other 3 cases. All 4 children had a ruddy complexion and the only physical abnormality noted was the presence of Little's disease in Case 2. The bleeding time,

coagulation time, clot retraction, platelet count and icteric index were within normal limits in all cases. Spectroscopic examination failed to reveal the presence of abnormal pigments.

Table 2 shows that there was no significant alteration in the erythrocyte count, hemoglobin content, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration of 7 of the members of the family (Cases 5 to 11). In contrast to these normals there are rather marked changes in the blood pictures of Cases 1 to 4. These 4 children had erythrocyte counts ranging from 7.48 to 8.80 million per c.mm., and hemoglobins ranging from 21 to 24.3 gm. per 100 cc. of blood. The hematocrits are approximately 150% of normal. The mean corpuscular volumes, mean corpuscular hemoglobins and mean corpuscular hemoglobin concentrations were within normal limits.

TABLE 2.—ERYTHROCYTE PICTURE.

Case No.	Age, yrs.	Sex.	Erythrocytes, mil./c.mm.	Hemoglobin, gm./100 cc.	Hematocrit, %.	Mean corpuscular volume, cu. μ.	Mean corpuscular hemoglobin, micro-microg.	Mean corpuscular hemoglobin concentration, %.
1	11	F	8.80	24.3	65	74	27.6	37.4
2	13	F	7.80	21.0	64	77	27.0	32.8
3	16	M	7.60	22.0	69	91	29.0	31.8
4	18	F	7.48	22.0	61	82	29.4	36.0
5	7	M	5.01	13.8	38	76	27.5	36.3
6	9	M	5.51	12.5	41	74	22.7	30.5
7	19	F	4.29	14.5	36	83	33.8	40.3
8	23	F	4.63	14.0	38	82	28.0	37.0
9	25	F	4.27	12.8	41	96	29.0	31.2
10	45	F	4.50	13.7	37	82	30.4	37.0
11	49	M	4.21	16.0	40	95	37.7	40.0

Chart 1 graphically illustrates the results of the blood volume studies. The circulating cell volumes of Cases 5 to 11 with normal red counts show normal circulating cell, plasma and total circulating blood volumes. The 4 children with the high erythrocyte counts (Cases 1 to 4) had marked increases in the volume of circulating cells per kilo of body weight. In Cases 1, 2 and 4, the increase in circulating cell volume was approximately double the normal value and occurred at the expense of the circulating plasma volume since the circulating cell volume increased without increase (above normal) in the total circulating blood volume. In 1 case (Case 3) the circulating cell volume was as great as the *total* circulating blood volume (three times as great as the normal circulating cell volume) of any of the other patients examined. This patient

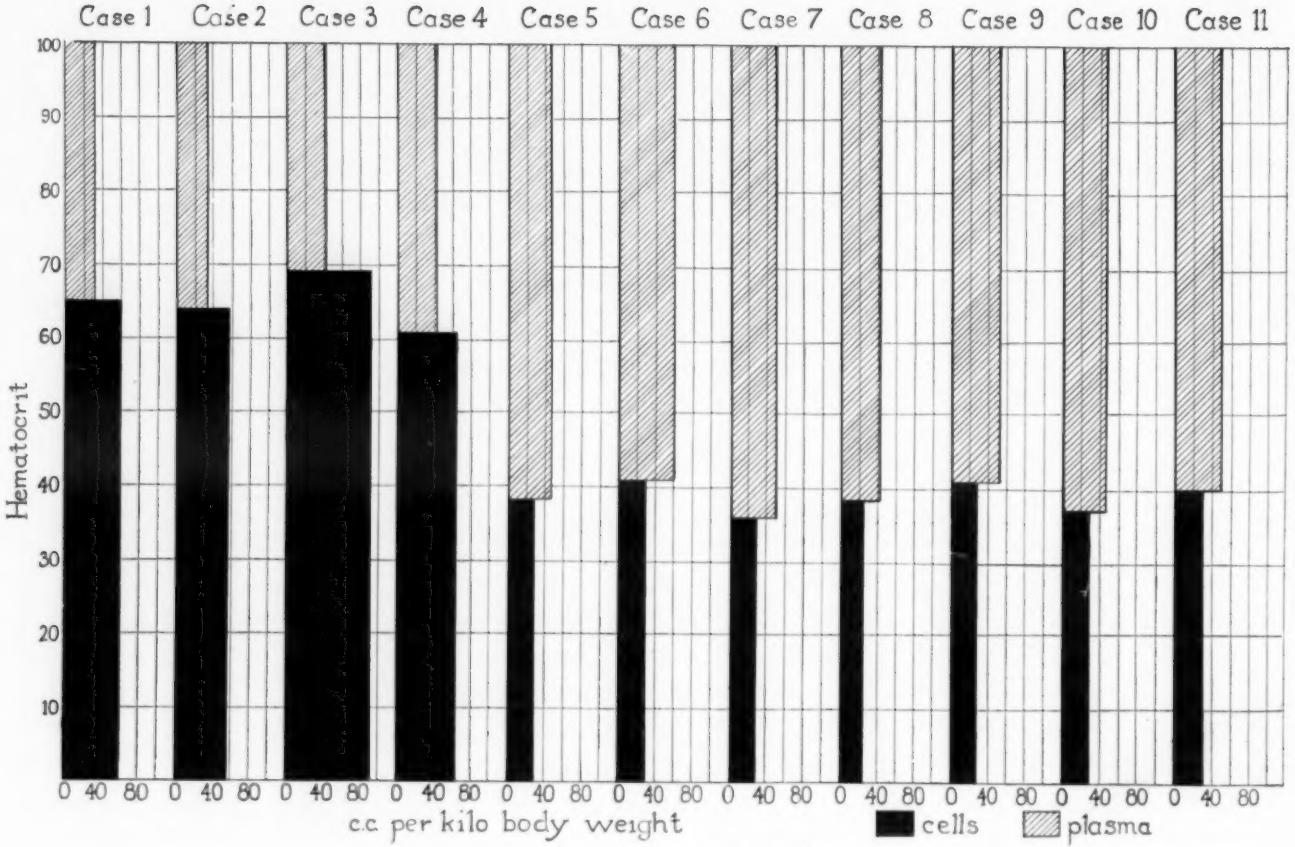

CHART 1.—Blood volume studies

had a total circulating blood volume 133 cc. per kilo of body weight. The greatly increased circulating cell mass is a common characteristic of Cases 1, 2, 3 and 4, and satisfy the criteria recently laid down by Haden[10] for the diagnosis of polycythemia vera.

In contrast to the common finding of leukocytosis with preponderance of neutrophils in polycythemia vera, our cases (Table 3) showed normal or subnormal leukocyte counts with no abnormality of the differential pattern. Similar blood pictures are found in the majority of cases of familial polycythemia reviewed in this paper. Sporado and Forkner,[21] *e. g.*, found essentially normal leukocyte and differential counts. It would appear that the factor (or factors) increasing the level of circulating erythrocytes accomplishes this purpose without interfering with the level of circulating leukocytes.

TABLE 3.—LEUKOCYTE PICTURE.

Case No.	Total leukocytes per c.mm.	Neutrophils, %.	Eosinophils, %.	Basophils, %.	Small lymphocytes, %.	Large lymphocytes, %.
1	7200	60	2	2	30	6
2	4800	63	2	1	30	4
3	4800	62	3	0	34	1
4	4600	45	5	1	47	2
5	6500	38	5	0	51	6
6	6800	65	0	0	32	3
7	7200	63	2	1	30	4
8	7300	61	3	0	36	0
9	5100	62	0	1	31	6
10	6500	63	1	0	28	8
11	8400	55	0	0	43	2

The blood sugar, non-protein nitrogen and serum proteins were normal, although the latter tended to approach the upper limit of normal. Isaacs[13] reported a high blood uric acid (6.9 mg. %) in a case of polycythemia vera and pointed out that the level of endogenous uric acid metabolism may be raised in this disease because of disintegration of the nuclei of not only the leukocytes but also of the erythrocytes. The blood uric acid was normal in our patients. Increased endogenous formation of uric acid need not be expected in untreated cases of polycythemia vera for if the level of circulating blood cell mass is established, the rate of destruction of erythrocytes may be no faster than in the normal individual; on the other hand, dramatic reduction of the circulating cell mass by methods increasing the breakdown of cell (phenylhydrazine, Roentgen ray, etc.) may be associated with high levels of blood uric acid.

TABLE 4.—BLOOD CHEMICAL FINDINGS.

Case No.	Non-protein nitrogen, mg. %.	Sugar, mg. %.	Uric acid, mg. %.	Serum calcium, mg. %.	Serum protein.		
					Alb., gm. %.	Glob., gm. %.	Total, gm. %.
1	40	83	2.18	10.5	5.05	2.73	7.78
2	30	80	3.00	10.2	4.00	2.80	6.80
3	34	85	2.80	9.8	4.30	2.92	7.22
4	28	75	2.23	10.0	4.10	3.10	7.20

CHART 1.—Blood volume studies

The serum calcium findings of Brown and Roth[4] prompted us to do serum calcium and serum protein determinations. Brown and Roth found hypercalcemia, 11.1 to 18.1 mg. % (average 14.3 mg. %) in a series of cases of polycythemia studied at the Mayo Clinic. They noted further that following reduction of the number of circulating erythrocytes (by phenylhydrazine therapy) they obtained normal or subnormal serum calcium values. They offered no convincing explanation for the hypercalcemia. Rabinowitch[18] and Benedict and Turner[2] failed to find hypercalcemia in polycythemia vera. The serum calciums in our cases were within normal limits.

Summary. Four cases of polycythemia occurring in one family are described. Data on the circulating blood volume in familial polycythemia are reported for the first time. Since cases of familial polycythemia seem to differ from classical cases of polycythemia vera in that elevated metabolic rate, neutrophilic leukocytosis, splenomegaly and symptoms referable to this disease are not a striking feature of familial polycythemia, it has been assumed that familial polycythemia is not the same as polycythemia vera. In these cases of polycythemia, however, the red cell mass was of the magnitude of that found in polycythemia vera. Since Haden[10] finds increase in cell mass to be characteristic of polycythemia vera, it now seems justifiable to include "familial polycythemia" in the group of cases of polycythemia vera.

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INFLUENCE OF THE PERIPHERAL CIRCULATION IN THE UPPER EXTREMITY ON THE CIRCULATION TIME AS MEASURED BY THE SODIUM CYANIDE METHOD.

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Although the circulation time has been studied by a variety of methods in the last few years the influence of the capillary circulation on the velocity of the venous return to the heart has been neglected. In the sodium cyanide, histamine, saccharine, calcium gluconate and decholine methods the reagent is usually injected into the antecubital vein and the length of time that it takes the injected substance to travel from the site of injection to the reacting organ is determined; sodium cyanide measures the antecubital to carotid sinus time.[3a] When the antecubital vein alone is used as the site for injection, these methods do not separate the elbow to heart circulation time from the heart to reacting organ time.

It is well known that local conditions can influence the peripheral circulation in the parts drained by the antecubital veins, namely, the forearm and hand, without appreciably altering the circulation of the body as a whole. Thus if slowing of the total blood flow in one forearm and hand appreciably decreases the velocity with which blood from these regions returns to the heart, the circulation time as measured from this extremity will be prolonged though no pathologic disturbance of the circulation is present. The object of this study was to determine whether changing the amount of blood flowing through the upper extremities by varying the local temperature would appreciably alter the antecubital to carotid sinus circulation time as measured by the injection of sodium cyanide.

Method. The circulation time was determined by the sodium cyanide method as described by Robb and Weiss:[3a] From 0.2 to 0.4 cc. of a 2% solution of sodium cyanide (4 to 8 mg.) was injected into one of the antecubital veins. The time elapsing between the injection and the first deep breath was recorded by a stop watch. The upper extremities were placed at heart level and the peripheral circulation was varied by placing the hands in plethysmographs containing water which could be maintained at any desired temperature. When one extremity was to be kept warmer than the other, measurements were not made until the difference in temperature of the forearms was detectable by palpation. When it was necessary to use

stasis to enter the vein, the injection was delayed until the reactive hyperemia induced by the venous occlusion had subsided. Sufficient time was allowed between determinations for the pulse rate to return to the resting level.

Results. The circulation times in 6 subjects are given in Table 1. Five of these subjects had normal cardiovascular systems; the sixth, G. K., had rheumatic heart disease with mitral regurgitation but no signs of decompensation. The circulation time in the cool arm in these 6 cases averaged 32.3 seconds and in the warm arm 18.5 seconds (average difference 13.8 seconds). The differences noted in Table 1 persisted as long as the hands and forearms remained at their respective temperatures, regardless of the number of determinations made. In each case the circulation time in the cool extremity was sufficiently prolonged to be considered pathologic by the usual standards. Robb and Weiss[3a] found that the cyanide circulation time in 35 normal subjects varied from 9 to 21 seconds; the average time was 15.6 seconds. In 5 of our 6 cases the circulation time as measured from the warm hand was within normal limits. In the sixth, F.R., a healthy male aged 22, the generalized constrictor effect of the cold water seemed to predominate and the circulation time in the warmer extremity in this subject was somewhat prolonged. An attempt was made to produce reactions of the same intensity from each arm by increasing the amount of cyanide injected in the cooler arm (Table 1). The reactions from the cooler arm, however, tended to be less intense than those obtained from the warmer arm with the more rapid peripheral circulation.

Discussion. The antecubital to heart circulation time is greatly influenced by the condition of the circulation in the portion of the forearm and hand that is drained by the antecubital veins. It is not clear whether the circulation in the forearm or in the hand, singly or combined, is of paramount importance in influencing the circulation time. Grant and Pearson[2] have shown that on moderate heating of the body vasodilatation occurs chiefly in the hand and that the forearm shows little increase in flow. Since the venous return from the hand passes through the forearm veins, however, an increase in flow in the hand alone is reflected by an increase in the amount of venous blood flowing through the forearm.

TABLE 1.—CIRCULATION TIMES AS DETERMINED BY INJECTION OF SODIUM CYANIDE IN THE ANTECUBITAL VEINS. EFFECT OF LOCAL TEMPERATURE OF UPPER EXTREMITY.

	Cool hand.			Warm hand.		
Subject.	Temperature of hand (C.).	Cc. of cyanide solution.	Circulation time (sec.).	Temperature of hand (C.).	Cc. of cyanide solution.	Circulation time (sec.).
F. C. R. . .	25°	0.40	47	40°	0.25	27
E. M. . . .	25°	0.35	30	40°	0.30	18
G. K. . . .	24°	0.40	35	40°	0.20	19
E. S. . . .	30°	0.30	25	40°	0.20	16
A. S. . . .	23°	0.35	30	43°	0.25	13
H. F. . . .	24°	..	27	42°	..	18

It will be noted that there was considerable variation in the circulation time in the warm arms. No attempt was made to duplicate standard conditions for each experiment. The hand temperatures and the length of time that the hands were immersed in the water varied in different experiments. In addition, the room temperature was not controlled. As the circulation time was determined from both the right and left antecubital veins within the space of a few minutes, each subject served as his own control to show that the difference in circulation time from the right and the left antecubital veins resulted from local changes in the peripheral circulation and not from gross changes in the general circulation.

Blumgart and Weiss[1b] in their study of the antecubital to heart circulation time in normal subjects by the radium C method found that the average elbow to heart time varied in normal subjects from 2 to 14 seconds. They also noted that the variation in the velocity of the venous blood in the arm in the same subject at different times and in different subjects was greater than the variation in the velocity of blood flow through the lungs. Robb and Weiss[3b] also found that in normal subjects an index of velocity of venous blood returning from the elbow, determined by measuring both the antecubital to carotid and the jugular to carotid circulation times by the injection of sodium cyanide, showed more variation than the jugular to carotid circulation time. These variations may well have occurred, at least in part, because the local temperature of the arm was not controlled.

The amount of sodium cyanide required to produce a clear-cut response depends on the rapidity of the circulation and the sensitivity of the carotid sinus. In our subjects, assuming the carotid sinus sensitivity to be constant over a short period of time, the amount required to produce a definite response varied with the temperature of the upper extremity. In the cooler arm with the slower peripheral circulation there was more time for dilution of the sodium cyanide solution during its passage to the heart and therefore larger doses were necessary. Likewise in subjects whose circulation times are prolonged because of cardiac failure, larger doses of radium C[1] or of histamine[5] are required than in normal subjects with a more rapid circulation. Robb and Weiss,[3b] however, called attention to the fact that the amount of sodium cyanide needed to produce a definite response in subjects with cardiac failure is only approximately three-fourths that required by normal subjects. They pointed out that in congestive failure an increased irritability of the respiratory center to cyanide usually more than compensated for the greater "stringing out" of the sodium cyanide caused by the slow circulation.

Over a period of years a few normal subjects have been encountered in whom satisfactory responses to sodium cyanide were not obtained.[4] In some of these subjects, a satisfactory response was obtained on the following day, indicating that the carotid sinus was sensitive to

cyanide stimulation. In these cases, the lack of response may have been due to a marked decrease in peripheral blood flow resulting from reflex arteriolar constriction of emotional origin. It is also possible that in certain instances the cyanide itself produces local irritation and spasm in the vein used for injection.

These observations show that the local temperature of the extremities plays an important part in determining the velocity with which blood returns to the heart. Before a given circulation time obtained by the injection of sodium cyanide into the antecubital vein can be considered as indicative of cardiac or other change, one must be certain that prolongation is not the result of a decrease in the peripheral blood flow induced by cold extremities.

Summary and Conclusions. 1. In 6 subjects the elbow to carotid sinus circulation time was measured in each arm by the sodium cyanide method. The two upper extremities were kept at different temperatures by immersing one hand in water at 40 to 43° and the other hand in water at 23 to 30° C. The circulation time in the cool arm averaged 32.3 seconds; in the warm arm 18.5 seconds.

2. The state of the peripheral circulation in an extremity influences the velocity of venous flow. Therefore, in an accurate study of the circulation time from the antecubital vein the temperature of the upper extremity must be controlled.

The authors wish to express their sincere appreciation to Dr. Soma Weiss for his many helpful suggestions and guidance in this work, and to Miss Sophia M. Simmons for her technical aid.

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RENAL ARTERIOLONECROSIS WITHOUT PAPILLEDEMA.

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It is a well-known clinical fact that the differential diagnosis between the terminal uremia of glomerulonephritis and that due to necrotizing nephritis (renal arteriolonecrosis) is extremely difficult.[6]

There is hardly one symptom or sign of renal dysfunction present in one that cannot be present in the other, such as hyperchromic microcytic anemia, uremic pericarditis, ulcerative colitis or azotemia. Even with respect to age incidence the two conditions overlap, for it must not be forgotten that renal arteriolonecrosis occurs like glomerulonephritis in middle age, early adult life and also in children.[5]

In contrast to the many equivocal diagnostic findings mentioned above, the presence of papilledema is regarded by some authors[1–4] as pathognomonic of renal arteriolonecrosis (necrotizing nephritis). Fishberg[2] goes so far as to state that without papilledema the diagnosis of renal arteriolonecrosis is not justifiable. Although we concede that the retinal vessels are the mirrors *par excellence* of the status of the kidney arterioles, we cannot subscribe to the extreme view that without papilledema there can be no necrotizing nephritis.

Of the 5 cases at this hospital in the last 4 years which showed renal arteriolonecrosis at autopsy, only 2 had papilledema. In the other 3, the eyegrounds showed mild retinal arteriosclerosis, *but no papilledema.* This autopsy experience differs so from that of the school of Volhard and Fahr that we feel it worthwhile to publish in some detail the last 3 cases.

Case Abstracts. Case 1.—Malignant nephrosclerosis without papilledema. A. S. (No. 97254), admitted, December 18, 1937; died, January 18, 1938. A white female, aged 42, gave a history of hypertension and headaches for 5 years. She had precordial pain for many years, and shortness of breath for 2. She was admitted to Bellevue Hospital in October, 1937, complaining of dizziness and weakness of 3 weeks' duration and swelling of the eyes lasting 3 days, associated with fever and increased dyspnea. At this time, her blood pressure was, systolic 272, diastolic 140, N.P.N. 35, and the urine showed a few red and white blood cells. She was discharged, November 20, 1937, with the diagnosis of hypertensive cardiovascular disease; secondary anemia, cause undetermined.

Five days before admission she first noticed bloody urine with polyuria and nocturia, being forced to awake 5 or 6 times a night. With the onset of hematuria, the patient complained of severe frontal headaches and impairment of vision by "black and green spots."

On physical examination the patient appeared drowsy. The heart was moderately enlarged to the left, with a harsh systolic murmur heard all over the precordium. The blood pressure was systolic 270, diastolic 170. The ophthalmologic consultant (Dr. F. S. Newman) found the "*retinal arteries extremely thin, thread-like and tortuous. Pallor of both discs show atrophy of secondary nature. No papilledema.*"

The urine showed a fixation of specific gravity between 1.010 and 1.014, innumerable red blood cells (4+ benzidine), many white blood cells, occasional hyaline and granular casts. R.B.C. 3,460,000, with 66% Hb.; N.P.N. was 94; total proteins 6.37; albumin-globulin ratio 1.26. Wassermann test negative. Roentgen ray showed concentric hypertrophy of the heart associated with sclerosis of the aortic arch. Cystoscopy revealed a low-grade cystitis that accounted for the bloody urine.

Radiant heat and light were applied to the kidney region, without any relief. Three days before exitus a rapidly developing parotitis appeared;

a pericardial friction rub was audible; urea frost covered the face and body, and the patient died, January 18, 1938.

Anatomic Diagnosis. (Condensed; Dr. Alfred Plaut): Malignant sclerosis of kidney (arteriolonecrosis); hypertrophy of left ventricle; arteriolosclerosis of different organs. Characteristic arterial changes in pancreas, intestinal canal, myocardium and uterus; diffuse hemorrhages in gastrointestinal tract; bronchopneumonia.

Kidneys each weigh 105 gm. The capsule is thin and strips with ease. Numerous small, pinhead hemorrhages are present on the pale, yellowish-pink, uniformly coarsely granular surface. On sections, the cortex of each kidney averages 5 to 7 mm. in width.

Microscopically. Corresponding to the granulation of the surface, atrophy of kidney tissue is found with fibrosis. In places, very severe hyaline droplet change is seen. Atrophy of tubules is widespread. A number of glomeruli show more or less necrosis and overgrowth of the capsular epithelium. While in places the diseased glomeruli form groups, the distribution appears entirely irregular in others, with normal and severely diseased glomeruli close to each other. Corresponding to the hemorrhagic spots, glomeruli are seen which are almost entirely destroyed by hemorrhage. Tubules in the surroundings of these glomeruli are widely distended with blood. In spite of some search, no hemorrhagic or necrotic lesions are found in the arterial vessels of the kidneys, the picture being principally that of atherosclerotic intimal thickening. The smallest arteries and afferent vessels show diffuse, very severe arteriolosclerosis with much necrosis. Arteriolonecrosis is likewise found in the cut sections of the ovary, uterus, myocardium, intestines, and is unusually marked in the liver, pancreas and hypophysis.

Comment. Pathologically, this case is of interest (Fig. 1) because of the widespread distribution and the severity of the arteriolonecrosis, without any signs of papilledema. The pathologic picture is characteristic of necrotizing nephritis, and the clinical diagnosis too would have been the same if the absence of papilledema had not militated against it in our minds, and suggested the erroneous diagnosis of secondary contracted kidney due to glomerulonephritis.

Case 2.—Malignant nephrosclerosis without papilledema. S. B. (No. 76793), admitted, September 25, 1935; died, October 12, 1935. A 47-year-old white female, a known hypertensive for the past 10 years. One year ago she had a right hemiplegia from which she recovered. There was a year's history of polyuria and nocturia, and a week's history of generalized aches and pains, tremors and marked drowsiness.

On admission, the patient was disoriented with a urinous odor to the breath and twitching of the extremities. The heart was moderately enlarged. Gallop rhythm was occasionally heard, as was a pericardial friction rub. Blood pressure was systolic 260, diastolic 160, with little variation in level. The urine showed persistently albumin, many granular casts, many white blood cells and rare red blood cells. Specific gravity was fixed between 1.006 and 1.008. N.P.N. varied from 111 to 166. Spinal fluid was under normal pressure.

Dr. S. Slomka, the ophthalmologic consultant, reported "*thin and tortuous retinal vessels, otherwise eyegrounds are normal.*"

Intravenous magnesium sulphate failed to reduce the very high blood pressure. Urea frost appeared on the face, and the patient died on the seventeenth day of hospitalization.

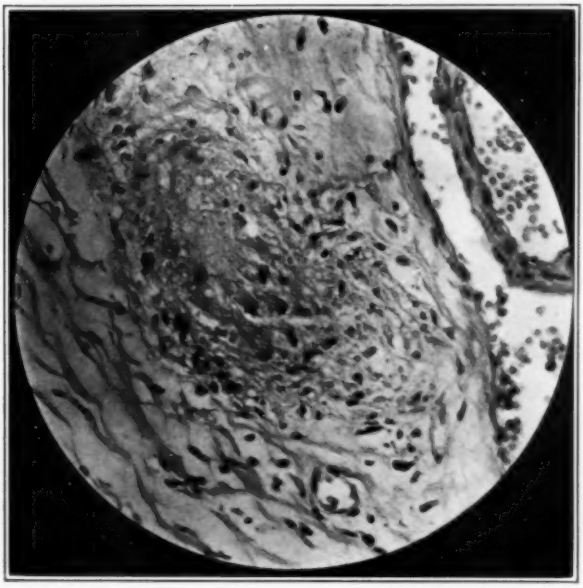

FIG. 1.—A necrotic arteriole in the stomach characteristic of lesions found in various organs. (The lesion in the stomach rather than the kidney is shown because the latter photographed poorly.)

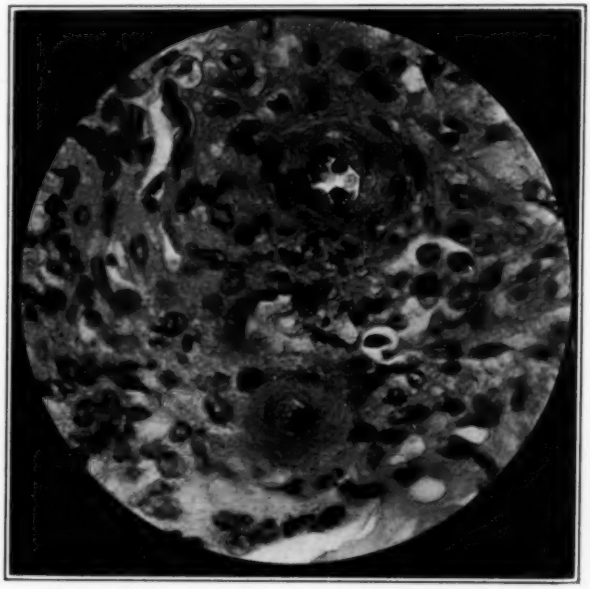

FIG. 2.—Necrosis in wall of renal afferent vessel. Fragments of chromatin visible.

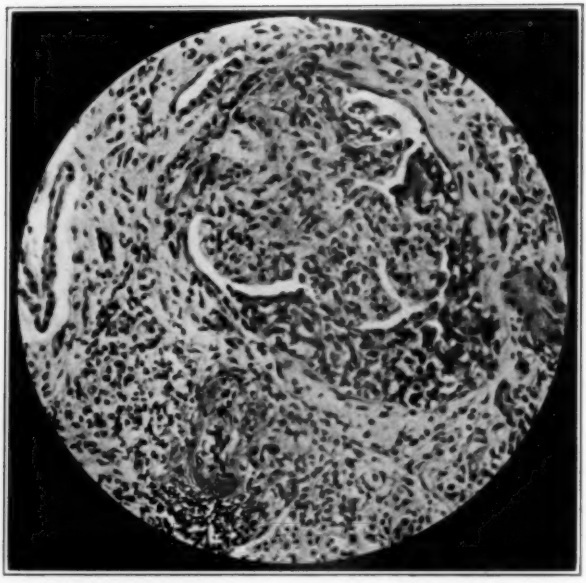

FIG. 3.—Necrotic afferent vessel. Thrombus with large crescent.

Anatomic Diagnosis. (Condensed; Dr. Alfred Plaut): Arteriolosclerosis of kidneys (malignant sclerotic type); hypertrophy of left ventricle; dilatation of left ventricle and auricle; mitral insufficiency; diffuse fatty change of myocardium; atheromatosis of sinuses of Valsalva, coronary arteries and ascending aorta; periarteritis nodosa in perisuprarenal fat tissue; multiple aneurysms of medium-sized arteries in the omentum; inflammatory process in myocardium; small scars of myocardium with isolated arteriolar lesion (perhaps rheumatic); moderate arteriolosclerosis of pancreas, suprarenals, intestine and uterus.

The kidneys are 75 and 100 gm. in weight. Both strip easily out of their thin, smooth capsules, leaving finely granular surfaces. The cut surfaces show very small cortices (0.4 cm. in width), and indistinct outline between cortex and medulla. There is much dark purplish-red mottling due to congestion and small hemorrhagic areas. The renal artery is thick-walled and shows atheromatous patches.

Microscopically (Fig. 2), the picture is that of arteriolosclerosis with much reduction in the number of glomeruli. There is necrosis of afferent vessels with severe fatty changes in these vessels and neighboring arteriolar portions. There is fatty change in many glomeruli but in few tubules. Some glomeruli show a breaking up of their tissue into hyaline droplets and amorphous hyaline pieces. Corresponding to hemorrhage seen on the surface, hemorrhage is found mostly within distended tubules. The largest arterial branches in the kidney give the ordinary picture of arteriosclerosis to different degrees. There is necrosis of small arteries not only in the kidney tissue proper but also in the hilar fat issue. One focus of acute periarteritis has been found (the one in the suprarenal fat tissue).

Comment. This case is of unusual pathologic interest in that it represents arteriolosclerosis and arteriolonecrosis of the kidneys with a focus of acute periarteritis nodosum in the suprarenal fat tissue. There is, however, no vascular lesion in the kidneys which in any way resembles periarteritis nodosum. The case is considered one of malignant nephrosclerosis, the arteriolar sclerosis and fibrosis being apparently much more extensive than the minimal changes in the eyegrounds would indicate. With a history of hypertension of 10 years' duration in a woman of 47, and with 1 year of threatened renal decompensation, finally with fixation of specific gravity and azotemia, the clinical picture of the terminal stage of malignant hypertension (necrotizing nephritis) was clear enough without investigation into the eyegrounds. The findings in the fundi were so meagre that several of the physicians who observed this patient did not dare venture the diagnosis of necrotizing nephritis which looked most probable from every other point of view.

Case 3.—Chronic glomerulonephritis and severe renal arteriolonecrosis without papilledema. R. B. (No. 62564), admitted, March 30, 1934; died, April 4, 1934). A 46-year-old white female with history of swelling of the face of 1 week's duration. She had hypertension at least 3 years, swelling of the feet for 2 years, frequent headaches, dizziness, dimness of vision and spots before the eyes for several months before admission. The present illness began 2 weeks after a mild upper respiratory infection with swelling of the face, hands and feet. Two nights before admission the patient became somewhat comatose, had numerous twitchings of the extremities, and did not void for 2 days.

The patient appeared to be *in extremis* from the start. There was a marked uremic odor to the breath. N.P.N. was 150; urine showed specific gravity 1.012, 4+albumin, many red blood cells and numerous white blood cells. Blood pressure was systolic 150, diastolic 105. Spinal tap revealed the spinal fluid under markedly increased pressure.

The ophthalmologic consultant (Dr. F. Newman) reported that "*aside from small attenuated vessels and occasional small petechial hemorrhages, the fundi are normal in all respects.*" The patient died 5 days after admission.

Anatomic Diagnosis. (Condensed; Dr. Alfred Plaut.) Chronic glomerulonephritis with severe arteriolonecrosis; arteriolonecrosis in liver; hypertrophy of left ventricle, subdural and subarachnoid hemorrhage; stasis in spleen, liver and lower lobes of lungs.

The kidneys weigh 135 and 140 gm. They strip with slight difficulty from their capsule, and are coarsely granular. The cortex is narrower than usual. The pyramids are short, dark purple with some red streaks. The renal arteries are thick-walled.

Microscopicallly (Fig. 3), the number of glomeruli in the later phase of glomerulitis is relatively small. All gradations are seen from glomeruli with only slight overgrowth to others where the capsular overgrowth represents the bulk of the glomeruli. There is distinct fatty change in the much distended tubules. On the other hand, in the blood-vessels the fatty change is scant. This is the more astonishing since *unusually severe arteriolonecrosis is found.* This necrosis is so marked that it is easily seen even on low magnification. Only a few of the necrotic arterioles are surrounded by inflammation. The small and medium-sized arteries mostly do not show severe lesions. Some of them have intimal proliferation. In several the media is very thick. Many irregular areas of fatty change are seen in the interstitial tissue.

A necrotic arteriole with inflammation similar to the one found in the kidney is seen in a section from the liver. Representative sections from myocardium, brain, aorta, and lung do not show arteriolonecrosis.

Comment. This is a case of chronic glomerulonephritis with such severe arteriolonecrosis that after the most careful microscopic study, the concomitant presence of both conditions had to be recognized.

Ophthalmologically in this case there was only thinning and attenuation of the retinal vessels and occasional petechial hemorrhages, otherwise the fundi were normal. Apparently there was no indication in the eyegrounds of the widespread arteriolonecrosis which took place in the kidneys and liver.

Discussion. It is not intended in the report of the above cases to belittle the importance of papilledema as the leading diagnostic sign in renal arteriolonecrosis due to necrotizing nephritis or other forms of hematogenous kidney disease. It brings out the important fact, however, that shortcuts in diagnosis and aphorisms may disturb rather than help our clinical thought. In all 3 cases at the bedside we felt the clinical picture was that of necrotizing nephritis, and the only hesitation about going on record with certainty as to the diagnosis was the absence of papilledema. We feel, therefore, that when the history and clinical manifestations favor the diagnosis of necrotizing nephritis, the absence of even so important a leading sign as papilledema should not deter us from making the diagnosis.

Another point of interest in our studies is that of the 5 postmortem cases proven to be necrotizing nephritis, the 3 which did not show papilledema were all females. Such a small series does not justify speculative reasoning. It suggests, nevertheless, that in arteriolar sclerosis and necrosis we may have a different selective affinity in the female than in the male. We know that arterial and arteriolar disease in general affects the two sexes differently, that coronary sclerosis is much more frequent in the male than in the female. This holds true for arteritis, thrombo-angiitis obliterans, and pulmonary arteriolitis. On the other hand, the cerebral vessels are affected a little more frequently in females than in males. It is possible, therefore, that the arteriolonecrotic process attacks the retina less frequently in the female than in the male. Thus renal arteriolonecrosis is less likely to be associated with papilledema in the female than the male.

Summary. Three cases are presented which showed at autopsy extensive arteriolar necrosis of the kidneys and which clinically failed to demonstrate even a faint suggestion of papilledema. All were females. In 2, the condition was pure necrotizing nephritis secondary to malignant hypertension. The third was a combination form where marked necrosis of the renal arterioles was engrafted on the picture of chronic glomerulonephritis.

These cases make untenable the clinical dictum that without papilledema there is no renal arteriolonecrosis.

We take this opportunity to express our indebtedness to Drs. I. W. Held and Alfred Plaut, without whose constant help this clinico-pathological study would have been impossible.

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CHANGES IN LACTIC ACID, pH AND GASES PRODUCED IN THE BLOOD OF NORMAL AND SCHIZOPHRENIC SUBJECTS BY EXERCISE.*

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The possibility that dysfunction in the oxidative mechanisms might play a rôle in the schizophrenic process has been suggested

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by previous investigations from these laboratories (Hoskins[4]). It has been shown that the blood volume per square meter body surface of these patients is smaller than that of normal men (Looney and Freeman[7a]) and that it circulates at a slower rate (Freeman[2]). It should be expected, therefore, that if the body tissues of the schizophrenic patient were metabolizing at a rate equal to the normal subject, differences in the oxygen and carbon dioxide content of the arterial and venous bloods of the two groups would be found. We (Looney and Freeman[7b]) have not been able to detect such differences and have therefore been forced to conclude that some disturbance in the oxidative functions must occur in the tissues. Further evidence of this dysfunction is seen in the inverse relationship which has been found to exist in our patients between the lactic acid and reduced glutathione content of the blood. We find that a fairly high correlation occurs between the two factors in the patients while no such relationship exists between them in normal subjects. This finding would seem to indicate that the removal of lactic acid is dependent on two or more catalysts, one of which is glutathione. In the patients, a disturbance of the other mechanisms throws a greater burden on the glutathione, and therefore a relationship between its level and that of lactic acid is found. In the normal subject, however, the glutathione can vary without affecting the lactic acid because of the presence of other mechanisms for its oxidation.

In order to gain further information concerning the production and removal of lactic acid we have studied the changes in its level in the venous blood following moderately strenuous exercise in 35 normal and 35 schizophrenic subjects. At the same time we have also determined the pH of the venous blood, and the oxygen and carbon dioxide content.

Method. The subjects, after resting for 30 minutes in bed, had a control sample of blood taken in an oiled syringe according to the technique of Looney and Childs.[6] They then ran up and down a flight of stairs 3.15 meters high for 10 minutes, making about 4 trips per minute. At the end of this period they again reclined in bed for 2 hours, and samples of blood were taken at 2 minutes, 4 minutes, 8 minutes, and so on, up to 128 minutes. The first and last samples after the exercise were taken in oiled syringes and the others in oxalated serum bottles.

The samples were analyzed for lactic acid in duplicate by the method of Friedemann, Cotonio and Shaffer[3] on 3 ml. of blood with the precaution that the air was drawn through wash bottles, the first containing bisulphite and the second acid permanganate, to remove any bisulphite binding and oxidizable substances. Blood gas determinations were made by the manometric method of Van Slyke. The pH determinations were made on whole blood at 38° C. with the glass electrode and electron tube potentiometer built according to the specifications of Stadie *et al.*[10]

Results. In Table 1 the results for the variables pertinent to the lactic acid production are tabulated. We find that there is a significant difference between the two groups with respect to age, body

weight, meters run in 10 minutes, kilogram meters of work performed, lactic acid produced per meter, and lactic acid produced per kilogram meter per minute.

TABLE 1.—THE EFFECT OF EXERCISE ON VARIOUS FUNCTIONS IN SCHIZOPHRENIC AND NORMAL SUBJECTS.

Variable.		N.	Min.	Max.	Mean.	Standard deviation.
Age	Pts.	35	18	48	26.6±1.0	5.6±0.64
	Nor. cont.	33	18	31	22.1±0.6	3.1±0.39
Body wt. (kg.)	Pts.	35	49	85	61±1.4	8.1
	Nor. cont.	35	56	82	68±1.2	6.9
Meters run in 10'	Pts.	35	85	154	110±2.8	16.2
	Nor. cont.	35	79	167	120±2.7	15.7
Kg./min.	Pts.	35	474	1064	690±24.6	143
	Nor. cont.	35	490	1091	812±19.5	114
Control L.A.	Pts.	35	6.3	18.2	12±0.5	3±0.36
	Nor. cont.	35	5.8	21.3	12.5±0.7	4.3±0.52
Max. L.A. reading	Pts.	35	22.9	147.6	77.37±4.20	24.5±3
	Nor. cont.	35	23.4	132.5	68.31±4.79	27.923±3.4
Increase of L.A. (mg.)	Pts.	35	11	135	65±4.2	24.4
	Nor. cont.	35	10	103	56±4.7	27.5
L.A. rise per meter	Pts.	35	0.12	1.53	0.6±0.04	0.25
	Nor. cont.	35	0.13	1.01	0.46±0.04	0.22
L.A. rise per kg. body wt.	Pts.	35	0.20	2.33	1.07±0.08	0.49
	Nor. cont.	35	0.16	1.78	0.81±0.08	0.44
L.A. rise per kg. m. min..	Pts.	35	0.02	0.26	0.097±0.007	0.04
	Nor. cont.	35	0.01	0.13	0.065±0.005	0.03

A consideration as to which of these variables might be expected to be of primary importance in relation to lactic acid production yields the following information. The difference in age, though significant, is not held to influence lactic acid production as there is no correlation between lactic acid and age in the age ranges observed in our samples.

The difference in weight is not brought about by the inclusion of extreme values, but is actually due to a tendency for the patients to be lighter than the normal subjects. This difference in itself would not be expected to alter significantly the lactic acid production, but it is of some importance in a consideration of the lactic acid production per kilogram meter of work performed. The patients, being lighter, would have had to run 13 more meters than the normal subjects to produce an equivalent amount of kilogram meters of work. This would amount to approximately one more

trip than the normal subjects made, whereas actually the patients averaged one less trip. As the number of trips made was significantly lower and the body weights were also significantly lower, it follows that the kilogram meters of work performed was, in turn, significantly lower. This value of 690 ± 24.6 kg./m./min. for the patients as compared with 812±19.5 kg./m./min. for the normal subjects was not due to the inclusion of a few extremely low values for the patients as contrasted with the normal subjects, but to a significant shifting of the distributions as a whole. Actually, 60% of the patients gave values of less than 700 kg./m./min.; whereas only 8.5% of the normal subjects fell below this figure. The mean of the control value of lactic acid for the patients of 12.02 mg. per 100 ml. of blood was almost identical with that of 12.51 mg. per 100 ml. for the normal subjects. The difference in the standard deviations is due to the fact that the values for the normal subjects were spread rather flatly throughout the entire range, while those for the patients were grouped together around the mean.

The increase in lactic acid was 65±4.2 mg./100 ml. for the patients against 56±4.7 mg./100 ml. for the normal subjects. This difference of 9 mg./100 ml. was not significant. It should be noted, however, that the number of meters run by the normal subjects was approximately 10% greater than the distance covered by the patients. As at this rate of exercise the lactic acid production is almost directly proportional to the work performed for any *given individual*, it follows that had each individual performed 10% more work the mean lactic acid would have been raised approximately 10% to 71 or 72 mg. and that the difference between the patients and the normal subjects would have been highly significant. For different individuals, however, there is no relation between the work performed and the amount of lactic acid produced when the exercise is moderate. Thus we find that the relation between lactic acid production and work performed by the normal subjects gives a correlation coefficient of only 0.38.

When the two groups are compared with respect to the lactic acid produced per meter run there is a significant difference between the patients with a mean value of 0.60±0.04 mg. and the normal subjects whose mean value was 0.46±0.04 mg. Likewise, on the basis of lactic acid produced per kilogram meter of work per minute the difference between the value of 0.097±0.007 mg. for the patients and 0.065±0.005 mg. for the normal subjects is highly significant.

These results give definite indication that the schizophrenic patients, as a group, show a marked muscular inefficiency in regard to lactic acid production for a given amount of work than does a group of normal subjects. The difference cannot, however, be ascribed to the schizophrenic process *per se* but only, at present, to the concomitant physical condition which can be expected in such a group. In this regard, it is to be noted that the normal

subjects were unemployed men who were hired to act as controls and lived in the same environment and received the same diet as the patients.

We have no means of determining the exact degree of training in the two groups, but some indication may be found in the fact that the changes in pulse rates taken in 23 members of each group showed no significant difference. Thus we find that the absolute rises in pulse rates per kilogram of work meter were 0.084 ± 0.008 for the patients and 0.069 ± 0.005 for the normal subjects.

The second question to be answered is whether the rate of lactic acid removal is essentially different in the normal and schizophrenic subjects. In order to determine this the means of the increases in lactic acid were plotted against time. As has been proven by the work of Margaria and his associates,[8,9] the lactic acid concentration after it has reached its maximum value decreases at a rate proportional to the excess of lactic acid in the blood. The curve which it traces is given by the equation:

$$L_t = 10^{a+bt}$$

where L_t is the excess concentration of lactic acid at time t after the maximum reading.

a is a constant which is determined by the maximum value reached by the lactic acid.

b is a constant which is always negative and is a measure of the rate at which the lactic acid is removed from the blood.

This formula does not hold immediately after the exercise ceases but begins to apply after about 4 minutes. In conformity with the findings of Margaria, Edward and Dill, we have found that in many instances the lactic acid concentration does not reach a maximum immediately on termination of exercise but may continue to increase for 4 to 5 minutes. For this reason we have taken for our initial value the maximum concentration of lactic acid and figured our time of recovery from this point. We have taken for our resting value the lowest point reached by lactic acid during the experiment. The observations were than fitted by the method of least squares to the curve $\log L_t = {}^{a+bt}$. The constants derived were then substituted in the original formula and gave the following equations:

For the normal subjects $L_t = 10^{1.74} - 0.015\ t$

and for the patients $L_t = 10^{1.80} - 0.013\ t$

The difference between the b coefficients for normal and schizophrenic subjects was found not to be statistically significant. The standard error of b was found to be 0.00137 for the normal subjects and 0.00109 for the patients.*

It would appear from a consideration of our values that the removal of excess lactic acid in human subjects at rest is fairly constant

* For the curve fitting I am indebted to Mr. R. Dorfman. The method of calculation involved in these determinations will be given on request to any interested readers.

and takes place at such a rate that one-half of the lactic acid of the body is removed in approximately 20 minutes. The value of the b constant of 0.015 ± 0.00137 for our 35 normal subjects agrees well with that given by Magaria and his coworkers[8,9] ranging from 0.015 to 0.020. While the production of lactic acid varies greatly with different individuals because of differences in muscular efficiency, degree of training, and so on, its removal during rest is independent of these factors.

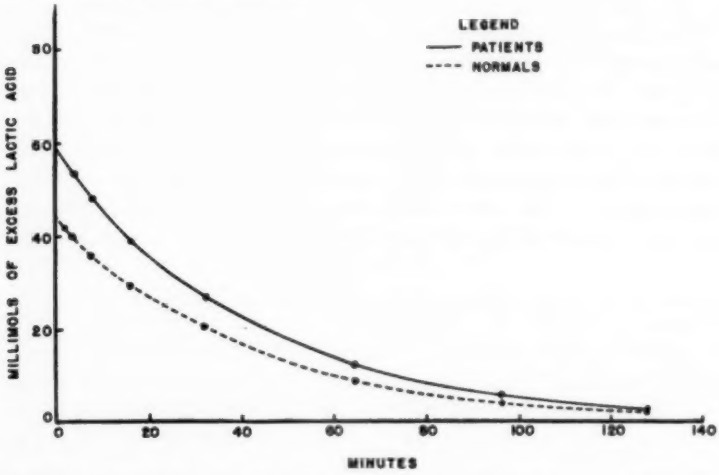

FIG. 1.—Rate of removal of lactic acid. ——— Patients $L_t = 10^{1.74 - 0.013t}$ ..... Normal $L_t = 10^{1.80 - 0.013t}$.

TABLE 2.—OXYGEN, CARBON DIOXIDE AND pH CHANGES DURING EXERCISE.

		Control reading, vol. %.	4 minutes after exercise, vol. %.	2 hours after exercise, vol. %.
O_2	35 patients	11.5	15.9	11.2
	35 normals	10.5	15.5	11.2
CO_2	35 patients	57.2	41.1	56.3
	35 normals	57.8	42.5	56.2
pH	35 patients	7.44	7.35	7.46
	35 normals	7.44	7.36	7.47

The changes in the oxygen and carbon dioxide content of the venous blood before and after exercise are given in Table 2. It will be noted that the values obtained for both normal and schizophrenic subjects are practically identical. In each case there was an increase in the oxygen content of the venous blood immediately after exercise. This change is unquestionably due to the more rapid circulation rate resulting from the exercise. In 2 hours the oxygen levels have returned to the preëxercise levels. The carbon dioxide levels decrease in both groups to about the same extent, the patients showing a decrease of 16.1 vol. % from the initial value of 57.2 vol. % and the normal subjects a drop of 15.3 from 57.8 vol. %. A high

inverse correlation was found to exist between the two gases, the coefficient for the patients being −0.80 and for the normal subjects −0.81.

Previously we have shown (Looney and Freeman[7b]) that under basal conditions there is a discrepancy in the relationship between venous oxygen and carbon dioxide in the patients as contrasted with normal subjects. We now find that this discrepancy has vanished after exercise. Whereas the normal subjects show no appreciable difference in the correlation coefficients in the two states, giving a value of $r = 0.76$ in the basal state and −0.81 after exercise; the patients, on the other hand, under the stimulation of the exercise give an increase in the coefficients from −0.47 in the basal state to −0.80. This is an example of the ability of the schizophrenic patient to become more like the normal subject as the result of a temporary stimulus.

The values obtained for the pH agree within 0.01 of a pH unit for schizophrenic and normal subjects both before and after exercise. The determinations were made by means of the glass electrode, which when checked with the hydrogen electrode on phosphate buffers agreed within 0.005 of a pH.

The fall in pH of 0.08 is somewhat more than that of 0.05 reported by Dill, Talbott and Edwards[1] for their 10 subjects, but can probably be accounted for by the difference in the work performed. Their subjects ran on the level at a rate of 9.3 km. per hour for 20 minutes and showed an average increase of about 25 mg. % of lactic acid, which was less than one-half of the average difference for our subjects. Similarly, their subjects showed a fall in carbon dioxide of 7.3 vol. % which was less than one-half that shown for ours. Within 2 hours after exercise the average pH had returned to slightly more alkaline levels than in the initial reading, the patients giving a value of 7.46 and the normal subjects one of 7.47.

The correlation coefficients given in Table 3 are derived from an analysis of covariance.* This technique permits obtaining estimates of the correlation which obtains on the average within an individual. Such an intra-individual correlation is biologically more meaningful than a group correlation, since biologic processes take place within the individual only (Jellinek[5]). The coefficients of Table 3 all refer to intra-individual relations. Since a common trend, such as created by the common factor of exercise, may create correlation between two biologically uncorrelated variables, or may at least boost the relationship far above the true inherent correlation, it becomes necessary to obtain estimates of the correlation which is independent from this trend. Such an estimate is obtained from the residual covariance. In the left-hand column are the net correlations between the variables after the trend due to the exercise is eliminated. This use of trend elimination is well

* I am indebted to E. M. Jellinek for the following correlation analysis.

illustrated in the case of the relationship between lactic acid and oxygen. As a result of the exercise both lactic acid and venous oxygen are increased. The uncorrected correlation coefficients found were 0.66 for the patients and 0.69 for the normal subjects. However, after correcting for the trend, we find that the coefficients for both the patients and the normal subjects have practically vanished. Thus we see that while the uncorrected coefficients would indicate a fairly high degree of relationship between lactic acid and oxygen content of venous blood, actually the two variables are completely independent of each other.

TABLE 3.—CORRELATION COEFFICIENTS AND REGRESSION EQUATIONS IN SCHIZOPHRENIC AND NORMAL SUBJECTS.

		Net intra-individual corrected for trend due to exercise.		Intra-individual uncorrected for trend.	
		r.		r.	
L.A. and CO_2	Pts.	−0.62	$CO_2 = 57.0 - 0.16$ L.A.	−0.95	$CO_2 = 59.9 - 0.25$ L.A.
	Nor. cont.	−0.81	$CO_2 = 58.19 - 0.21$ L.A.	−0.96	$CO_2 = 60 - 0.27$ L.A.
L.A. and pH	Pts.	−0.61	pH = 0.46 − 0.0015 L.A.	−0.92	pH = 0.47 − 0.0017 L.A.
	Nor. cont.	−0.64	pH = 0.48 − 0.0018 L.A.	−0.87	pH = 0.48 − 0.0018 L.A.
CO_2 and pH	Pts.	+0.12	pH = 0.36 + 0.001 CO_2	0.85	pH = 0.10 + 0.006 CO_2
	Nor. cont.	+0.58	pH = 0.10 + 0.006 CO_2	0.83	pH = 0.09 + 0.006 CO_2
CO_2 vs. O_2	Pts.	−0.54	$CO_2 = 60.2 - 0.67\ O_2$	−0.80	$CO_2 = 78.5 - 2.10\ O_2$
	Nor. cont.	−0.54	$CO_2 = 61.9 - 0.79\ O_2$	−0.81	$CO_2 = 76.8 - 1.99\ O_2$
O_2 vs. L.A.	Pts.	0.01	$O_2 = 12.3 + 0.001$ L.A.	0.66	$O_2 = 10.5 + 0.68$ L.A.
	Nor. cont.	0.12	$O_2 = 11.9 + 0.20$ L.A.	0.69	$O_2 = 10.2 + 0.76$ L.A.

It will be noted that the *uncorrected coefficients* in Table 3 are strikingly similar for both patients and normal subjects in regard to all variables. In the case of the relationship between lactic acid and carbon dioxide it was found that an increase of 1 m.Eq. of lactic acid was accompanied by a drop in carbon dioxide of 1 m.Eq. in the patient and 1.07 m.Eq. in the normal subjects. As the fall in total carbon dioxide occurs almost completely at the expense of the bicarbonate, and since Dill *et al.*[1] have shown that there is only a very slight change in the carbon dioxide tension of the blood during exercise, this would indicate that 1 mol. of bicarbonate was neutralized for each mol. of lactic produced. These findings do not agree with those of the above investigators as they recorded an increase in lactic acid of 1.57 m.Eq. as opposed to a drop of 2.11 m.Eq. in bicarbonate. It seems probable that this discrepancy may be accounted for by the difference in the severity of the exercise, the washing out effect from the increased ventilation playing a greater rôle when the exercise is less severe.

Here again the greater rigidity in the carbon dioxide system, shown by the patients in our previous studies (Looney and Freeman[7b]), is noted in the net intra-individual correlations, the patients showing a small degree of dependency and accounting for a smaller decrease in carbon dioxide for each millimol of lactic acid produced.

Even more striking is the difference shown between the carbon dioxide decrease and the fall in pH. Under exercise the two groups

give almost identical values for their regression equations and correlation coefficients; but when these are corrected for the trend due to exercise to give the net relationships which should exist under ordinary conditions, we find that the normal subjects show practically no difference in the regression equation but a lower correlation coefficient, 0.58 instead of 0.83. The b coefficient for the pH is not affected, a change of 0.0062 being given for each vol. % of CO_2 as against 0.0064 after exercise. The patients, on the other hand, show a very great difference in the two states. Under stress their performance is practically identical with that of the normal subjects, giving a correlation coefficient of 0.85 and a b coefficient in the regression equation of 0.0061. When the effect of exercise is eliminated the dependency of pH on CO_2 almost completely vanishes, the correlation coefficient becoming 0.12 and the change in pH becomes entirely unpredictable from the carbon dioxide values. The relationship between lactic acid and pH remains very similar for both patients and normal subjects and is relatively little affected by exercise.

Summary. The gases, pH and lactic acid were determined in the venous blood of 35 normal and 35 schizophrenic subjects before and after running for 10 minutes up and down stairs.

The mean of work performed by patients was 690 ± 24.6 kg./m./min., that for the normal subjects 812 ± 19.5 kg./m./min. The increase of lactic acid was 65 ± 4.2 and 56 ± 4.7 mg. respectively. The patients produced 0.097 ± 0.007 mg. lactic acid per kg./m./min. which was significantly higher than that of 0.065 ± 0.005 mg. for the controls.

The pH of the blood of the patients gave: control 7.44, after exercise 7.35, at end 7.46; of normal subjects 7.44, 7.36, 7.47. For the patients the O_2 values were 11.5, 15.9 and 11.2 vol. % and the CO_2 values 57.2, 41.1 and 56.3 vol. %; for the normal subjects the corresponding values were 10.5, 15.5 and 11.2 and 57.8, 42.5 and 56.2 vol. %.

The rate of disappearance of lactic acid was the same for both groups and dependent only on the blood level. Equations fitted to the curve for removal of lactic acid were $L_t = 10^{1.80-0.013t}$ for the patients and $L_t = 10^{1.74-0.15t}$ for the normal subjects. For normal subjects, about one-half of the excess lactic acid will be removed in 20 minutes during rest after the exercise.

A high negative correlation was found between lactic acid and carbon dioxide, after exercise the coefficients being -0.95 for the patients and -0.96 for the normal subjects. Between lactic acid and pH a similar effect was found with coefficients of -0.92 for patients and -0.87 for normals. While the high correlation 0.85 between CO_2 and pH appearing in the patients after exercise nearly vanishes when the trend due to exercise is eliminated, that in the normal subjects is relatively little affected.

As a result of the stress from exercise the carbon dioxide mechanisms of patients tend to approach more nearly the action of the normal subjects.

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THERAPEUSIS OF EXPERIMENTAL TYPE I PNEUMOCOCCIC MENINGITIS IN RATS.

COMPARATIVE THERAPEUTIC RESULTS OBTAINED WITH SULPHANILAMIDE, SERUM, AND COMBINATION THERAPY.

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HERETOFORE therapeusis of experimental pneumococcic meningitis involving lavage through quadruple puncture[26a,b] or intracarotid injection of antiserum-optochin mixtures[15] while showing promise, has not been very successful. Adaptations of these experiments and other forms of treatment, have not significantly altered the mortality of clinical pneumococcic meningitis as judged by recent reviews of the subject.[11,28,29] Within the last year, however, reports[1,3,7,14,16,17,19,21–23,27,30] of cures with sulphonamide compounds in 23 cases of pneumococcic meningitis have renewed hope for an effective treatment.

Additional support for this outlook is to be found in the generally favorable results obtained with sulphanilamide therapy in experimental pneumococcic infections.[6b] Although this therapeutic action is not of as high an order as that observed against infections caused by hemolytic streptococci or meningococci, and is more pronounced

in rats and rabbits than in mice, it has been consistently effective in pneumococcic pneumonia[5a,b,9a,b] and peritonitis[24] in rats.

More recently, we[6,10] have shown that sulphanilamide therapy in Type II pneumococcic meningitis of rats resulted in 54 to 73% survivals, whereas none of the untreated rats survived. Inasmuch as it has been demonstrated[4,5b,9b] that therapy with sulphanilamide plus specific antiserum gave better results than either therapeutic agent alone, it was thought of interest to use this combination therapy in experimental pneumococcic meningitis of rats. Accordingly, this report presents results obtained in Type I pneumococcic meningitis of rats treated with (*a*) sulphanilamide, (*b*) horse antipneumococcic serum, (*c*) rabbit antipneumococcic serum, and (*d*) a combination of sulphanilamide and rabbit serum.

Method and Results. Meningitis was produced by intracranial inoculation of a properly diluted 18-hour broth culture of a Type I (Neufeld) pneumococcus. A 3 mm.-long, 25-gauge needle, attached to a tuberculin syringe, was pushed to the hilt through skin and skull of etherized rats at a point about 4 mm. to the left of the sagittal suture and halfway between eye and ear. About 0.1cc. of the inoculum, which consisted of a 10^{-5} or 10^{-4} dilution of culture, was then slowly injected.

Data obtained in the present experiments confirmed previous work which demonstrated that meningitis and bacteremia were well established 6 hours after the inoculation. Histologic sections of the brains of rats killed at various intervals following inoculation showed, in addition to ecchymoses, irregularly scattered, small foci of mononucleated cells and a few neutrophils in the pia. These were found as early as the second hour, at which time cultures from the lumbar region of the cord were generally positive. Treatment, consisting of 100 mg. of sulphanilamide orally, or 333 units of antiserum intraperitoneally, or both together, was administered after the bacteremia was established.

The following 3 experiments were performed:

I. Infection with slightly less than 10 fatal doses and initial treatment delayed 7 hours following infection.

II. Infection with about 10 fatal doses and initial treatment delayed 12 hours following infection.

III. Infection with about 100 fatal doses and initial treatment delayed 7 hours following infection.

I. *Infection with slightly less than 10 fatal doses and initial treatment delayed 7 hours following infection:*

A series of 58 rats was inoculated with a 10^{-5} culture dilution, as described above. In addition, 2 rats were inoculated with a 10^{-6} dilution and 3 with a 10^{-7} dilution of the same culture for the purpose of titration. Both 10^{-6} and one of the 10^{-7} rats were dead in 5 days.

The infected animals were divided into 4 groups of 11 each and a control group of 14. All treatments were begun 7 hours following infection. One group was treated orally with 100 mg. of sulphanilamide* twice a day for 2 days and once daily for 6 more days. A second group received 333 units of horse antiserum† intraperitone-

* Kindly supplied by the Monsanto Chemical Company, St. Louis, Mo.

† Kindly supplied by E. R. Squibb & Sons, New York.

ally, followed by similar treatments on the second and third days. The third group was similarly treated with concentrated rabbit antiserum.* The fourth group was treated with a combination of sulphanilamide by mouth and rabbit serum intraperitoneally as in the groups where these therapeutic agents were used alone.

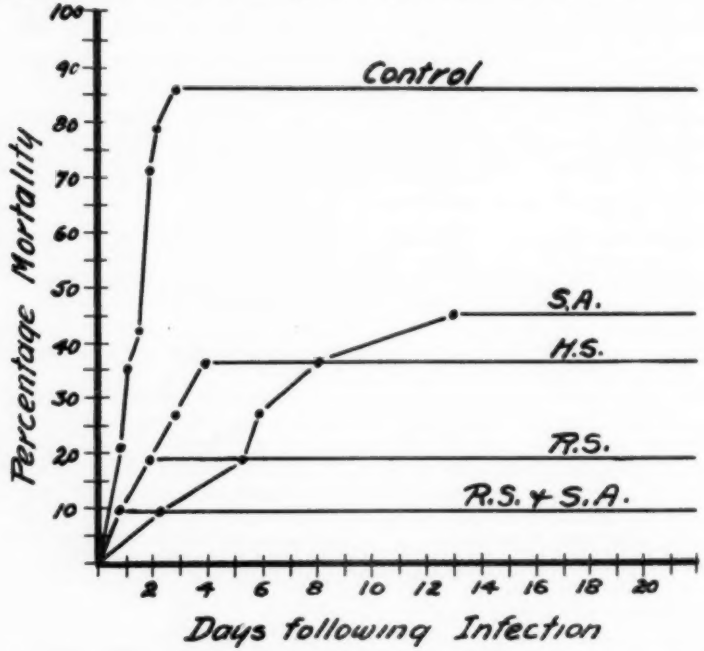

FIG. 1.—MORTALITY CURVES OF RATS INFECTED WITH LESS THAN 10 FATAL DOSES OF TYPE I PNEUMOCOCCUS AND TREATED 7 HOURS FOLLOWING INFECTION.

Infection: 0.1 cc. of a 10^{-5} broth dilution of an 18-hour broth culture intracranially. *Treatment:* Controls: 14 rats, no treatment. S. A.: 11 rats, 100 mg. of sulphanilamide orally twice daily for 2 days and once daily for 6 following days. H. S.: 11 rats, 333 units of horse antipneumococcus serum intraperitoneally for 3 successive days. R. S.: 11 rats, 333 units of rabbit antipneumococcus serum intraperitoneally for 3 successive days. R. S. and S. A.: 11 rats, combination of rabbit antipneumococcus serum and sulphanilamide therapy used in R. S. and S. A. above.

Results. The results are shown graphically in Figure 1. The mortality rate of the control group was 85.7%; of the sulphanilamide group, 45.5%; of the horse serum group, 36.4%; of the rabbit serum group, 18.2%; and of the combination treatment group, only 9.1%. Fatalities in the sulphanilamide group showed a greater increase in survival time than was seen in the other groups.

II. *Infection with approximately 10 fatal doses and initial treatment delayed 12 hours following infection:*

A series of 60 rats was infected with a 10^{-5} culture dilution as in the preceding experiment. Three titration rats, given one-tenth of

* Kindly supplied by E. R. Squibb & Sons, New York.

the infecting dose, died in 46 to 94 hours, whereas only one titration rat of 3 given one one-hundredth of the infecting dose died (51 hours). Positive cultures were obtained from the spinal cords (distal lumbar portion) and heart blood of 5 infected rats killed at the time treatment was begun.

The remaining 55 rats were divided into 4 groups. One group of 13 served as untreated controls, a second group of 14 was treated

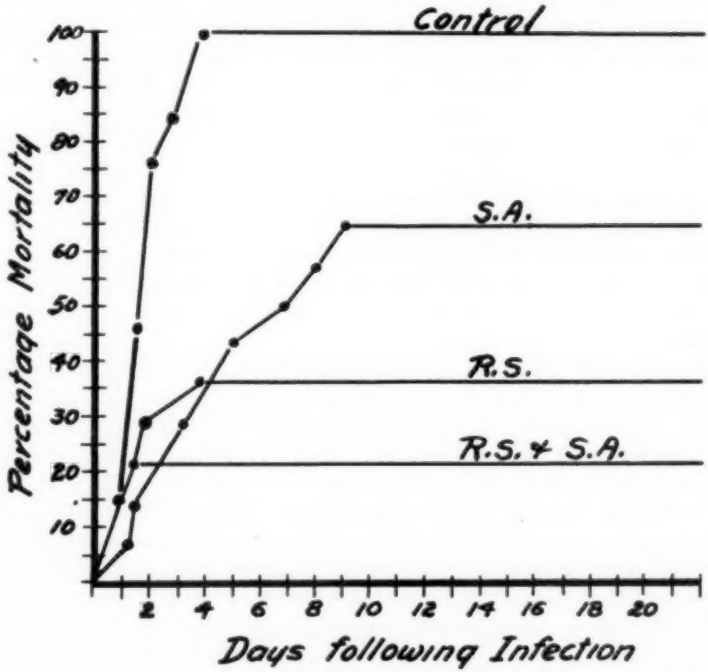

FIG. 2.—MORTALITY CURVES OF RATS INFECTED WITH APPROXIMATELY 10 FATAL DOSES OF TYPE I PNEUMOCOCCUS AND TREATED 12 HOURS FOLLOWING INFECTION.

Infection: 0.1 cc. of 10^{-5} broth dilution of an 18-hour broth culture intracranially. *Treatment:* Controls: 13 rats, no treatment. S. A.: 14 rats, 100 mg. of sulphanilamide twice daily for 3 days and once daily for 3 following days. R. S.: 14 rats, 333 units of rabbit antipneumococcus serum intraperitoneally for 3 successive days. R. S. and S. A.: 14 rats, combination of rabbit antipneumococcus serum and sulphanilamide therapy used in R. S. and S. A. above.

with sulphanilamide, a third group of 14 was given rabbit serum, and the remaining 14 rats were treated with a combination of rabbit serum and sulphanilamide. The first treatments in each group were given 12 hours following infection. The rabbit serum was given intraperitoneally in 3 equal doses on 3 successive days to a total of 1000 units. Sulphanilamide was administered orally in 100 mg. doses twice daily the first 3 days and once daily for 3 more days.

Results. A graphic representation of the results is given in Figure 2.

All of the 13 untreated animals were dead in less than 4 days. The sulphanilamide group suffered a 64.3% mortality, while in the rabbit serum group only 35.7% died and in the combination treatment group only 21.4% succumbed.

III. *Infection with approximately 100 fatal doses and initial treatment delayed 7 hours following infection*:

A series of 84 rats was infected as in the two preceding series except that the inoculum was 10 times more concentrated (10^{-4}). Cultures of the blood and distal lumbar portion of the spinal cord of 6 of these rats which were sacrificed in pairs 2, 4, and 6 hours following infection were positive even in the 2-hour animals.

Treatments were begun 7 hours following infection. Sulphanilamide was administered orally to 21 of the rats in 100-mg. doses twice daily for 2 days and once a day for 2 more days. A second group of 21 animals was given rabbit serum intraperitoneally to a total of 1665 units per rat in 5 equal doses distributed over as many days. A third group of 21 rats was given a combination of these 2 treatments, while the remaining 15 animals served as untreated controls.

Results. All of the rats in the control group as well as in the sulphanilamide group died with insignificant differences in survival time. In the serum group, the mortality rate was 81%, while in the combination group only 57% died. A graphic representation of these results is shown in Figure 3.

Pathologic Changes in Brain and Cord. The surviving rats were killed 3 to 6 weeks after infection. Although grossly no recognizable changes were found, microscopically practically all rats showed a diffuse thickening of the brain pia associated with a scanty round cell infiltration. In addition, many animals showed deep cortical scars, foci of calcification, and hemosiderin deposits. The spinal cords showed little or no change. Only a few of the cords showed pial changes corresponding to those seen in the brain. These findings will be reported in detail in a subsequent publication.

Discussion. Under normal conditions antibodies present in the blood do not find their way into the spinal fluid, but in the presence of certain inflammatory changes a limited amount of immune substances may pass the barrier recognized to exist between the blood and the cerebrospinal fluid.[2,20] Sulphanilamide, on the other hand, is present in the cerebrospinal fluid in concentrations parallel to, but slightly less than, those of the blood in both health and disease.[2,18a,b,25] It appears probable that the past ineffectiveness of therapy in clinical pneumococcic meningitis may be due in part to the barrier which prevents antibodies injected into the blood stream from attaining effective concentrations in the spinal fluid. A second important factor is the viscid character of the exudate which favors blocks and

hinders a uniform distribution of intrathecally administered serum. Stewart[26a,b] working with pneumococcic meningitis of dogs found that dye injected over one cerebral hemisphere did not stain the other, and that it was necessary to bring antiserum (and optochin) into intimate contact with the exudate containing the microörganisms in order to obtain therapeutic results. In apparent opposition to this concept is the stand taken by Hoyne[13], who found intravenous

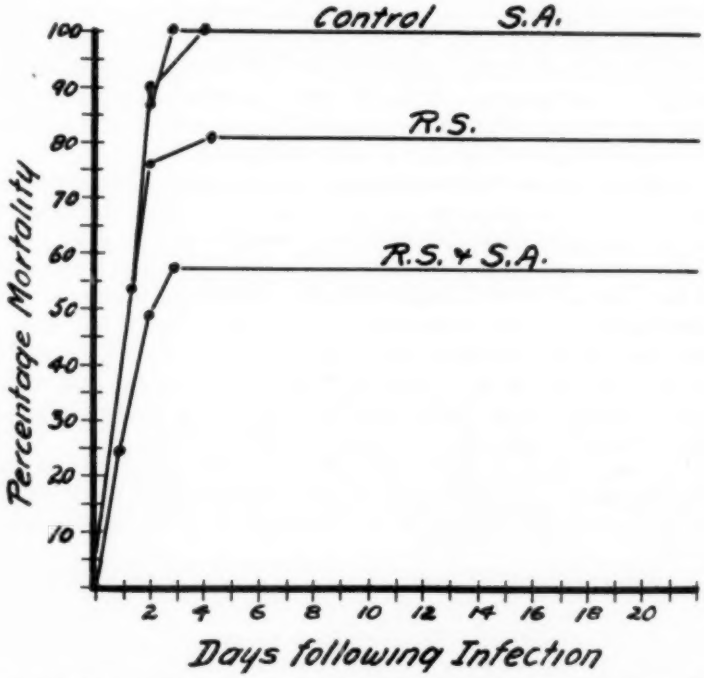

FIG. 3.—MORTALITY CURVES OF RATS INFECTED WITH APPROXIMATELY 100 FATAL DOSES OF TYPE I PNEUMOCOCCUS AND TREATED 7 HOURS FOLLOWING INFECTION.

Infection: 0.1 cc. of a 10^{-4} broth dilution of an 18-hour broth culture intracranially. *Treatment:* Controls: 15 rats, no treatment. S. A.: 21 rats, 100 mg. of sulphanilamide orally twice daily and once daily for 2 following days. R. S.: 21 rats, 333 units of rabbit antipneumococcus serum intraperitoneally for 5 successive days. R. S. and S. A.: 21 rats, combination of rabbit antipneumococcus serum and sulphanilamide therapy used in R. S. and S. A. above.

serum therapy effective in meningococcic meningitis. The latter disease, however, is considered by some to be primarily a bacteremia with meningitis as a complication.

The remarkable therapeutic success obtained in our experiments with specific antiserum administered intraperitoneally suggests that the so-called cerebrospinal barrier is very permeable to certain Type I antibodies in rats suffering from pneumococcic meningitis. There is

a possibility that this phenomenon may be a function of the effective size of the antibody molecule.[8,12*] This assumption may explain the superiority of rabbit serum over horse serum (Fig. 1) in spite of the apparently equal dosage.

Comparative results with sulphanilamide and specific serum therapy in experimental pneumococcic pneumonia[5b,9b] have indicated that sulphanilamide was at least as effective as serum therapy. The fact that the present results do not support our previous findings with horse antiserum may be due to differences inherent in the diseases, or the sera used, or to the fact that a 33% larger dose (based on a human adult dose of 350,000 units) was employed in the meningitis experiments. Although this superiority of horse antiserum over sulphanilamide was negligible, the rabbit antiserum was definitely more efficacious in all experiments.

The best results in each experiment were obtained by a combination therapy of rabbit serum given intraperitoneally and sulphanilmide by mouth. These findings are in complete harmony with conclusions previously drawn by us[5b,9b] and by Branham and Rosenthal[4] and they support the rationale of similar clinical procedures.[7]

Conclusions. 1. An experimental meningitis due to a virulent Type I pneumococcus has been produced in rats.

2. Sulphanilamide by mouth and antipneumococcic sera given intraperitoneally, were both effective in reducing the mortality of experimental pneumococcic meningitis in rats.

3. A combination of sulphanilamide by mouth and specific serum intraperitoneally was the most effective treatment, and showed a marked therapeutic effect even in the presence of an overwhelming infection.

4. Sulphanilamide therapy proved practically as effective as horse antipneumococcic serum therapy. Rabbit antipneumococcic serum was more effective than similar horse serum.

5. Delay in treatment or massive increase in the size of the infecting dose diminished the percentage of recovery irrespective of the treatments attempted.

* Another possible explanation, that of species differences, is ruled out by our more recent work with Type III pneumococcic meningitis in rats in which specific rabbit antiserum was completely ineffective. This work will soon be published.

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CONGO RED: TOXICITY AND SYSTEMIC ACTIONS.

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The increasing importance of Congo red as a diagnostic and therapeutic agent indicates the desirability of acquiring accurate information regarding its toxicity and general actions. Recent uses of the dye as a hemostatic[11] in pernicious anemia,[7,9] in infections,[1] and in experimental intoxications[3] indicate unusually diverse and interesting effects possessed by one substance. Therefore, it was thought desirable to supplement the present meager and incomplete pharmacological data on this dye with more detailed information. It is hoped that this will serve as a basis for the study of other interesting dyes of the same general group. This paper discusses the toxicity, fatal doses, cause of death and muscular actions in different animals.

Methods. The dye used was that marketed under the designation "Congo red 4B" (Coleman and Bell). Unless otherwise stated, the solution for injection was always prepared by dissolving 1% Congo red in a 5% aqueous solution of dextrose. The solution was boiled and then filtered through fine filter paper. When this solution was kept in a refrigerator, it maintained its colloidal properties and clear appearance almost indefinitely. On the other hand, Congo red in normal saline solution (0.85% NaCl) seldom remained stable longer than 12 to 24 hours due to a "salting out" effect of the sodium chloride. Some have used the Congo red dissolved in distilled water, but this is undesirable for parenteral administration because the solution is hypotonic.

Toxicity and Fatal Doses. The available data on the toxicity of Congo red are so limited[5,6,8,11] that it is difficult to draw accurate conclusions as to tolerated or fatal doses. We have extended the

data on a great number and variety of animals, *i. e.*, 249 pigeons, rabbits, rats and cats. The results should be helpful in obtaining an idea of the order of toxicity for humans. All injections were made intravenously.

The general symptoms of toxicity were similar in all species, except pigeons, which reacted rather rapidly and sometimes with convulsions. Immediately following the injection of a fatal dose of Congo red, the animals became depressed, and moved about the cage only when stimulated. Within a period of 1 to 24 hours, and depending on the species and dose, the depression passed into coma, and death supervened promptly. Respiration was practically unchanged until just before death, when periodic hypernea and apnea often occurred.

At autopsy, the blood was always fluid and did not clot after standing several hours. The heart was widely dilated, especially the ventricles. The lungs were congested, and occasionally there were subpleural hemorrhages. Histologically, there was widespread dilatation of capillaries, arterioles and venules; the hyperemia was especially marked in the kidneys and lungs, but to a less extent in the heart and liver. The lungs also showed occasional areas of extravasated blood.

The per cent mortalities according to varying doses of Congo red in different species are presented in Table 1. The highest tolerated single doses in mg. per kg. body weight were as follows: pigeons, 100; rats, 140; rabbits, 200; cats, 100. The doses causing 50% mortality in mg. per kg. were as follows: pigeons, 150; rats, 190; rabbits, 250; cats, 125. These doses were from 25 to 90% greater than the tolerated doses in the same species.

The results show considerable variation between species, thus making it difficult to predict the tolerance of the dye in humans. The highest reported single dose of the dye used clinically is 150 mg. or 2.5 mg. per kg. for a 60-kg. adult. This is only one-fortieth the maximum tolerated dose in pigeons and cats, the most susceptible species. Therefore, it would appear that the margin of safety in using Congo red intravenously is rather wide.

The absorption from intramuscular, subcutaneous and intraperitoneal injections in rabbits and pigeons was too slow and incomplete to give reliable results for toxicity. The absorption is to be described separately. Macht and Grumbein[6] have reported intraperitoneal fatal doses of about 200 to 400 mg. per kg. for mice, and death in these animals after subcutaneous injections for several days. Matsuo[8] reports the following unusually high fatal doses: frog, 2 mg. per gm. (lymph sac), and mouse, 1.5 mg. per gm. (method of administration not stated).

Toxicity According to Solvent. Since Congo red is often used clinically in purely aqueous or normal saline solutions, it was interesting to compare the toxicity of such solutions with Congo

red in 5% dextrose solution. Of 10 pigeons, injected with 160 mg. per kg., Congo red in distilled water, 5 died (mortality, 50%), whereas 8 of 10 other pigeons died (mortality, 80%) injected with 160 mg. per kg. in normal saline solution. The mortality results showed also that Congo red in distilled water was about as toxic as the dye in dextrose solution (Table 1), while Congo red in saline solution was more toxic. The higher toxicity of saline solutions is attributed to the flocculation of Congo red which occurs promptly in Congo red saline mixtures. Such flocculated solutions are obviously undesirable, if not dangerous, for intravenous injection in humans. Except when indicated, the following experiments were made with Congo red in 5% dextrose solution.

TABLE 1.—INTRAVENOUS TOXICITY OF CONGO RED.*

Dose, mg. per kg.	Pigeons.		Rats.		Rabbits.		Cats.	
	No.	Died, %.	No.	Died, %.	No.	Died, %.	No.	Died, %.
50	..	..	..	..	..	..	7	0
100	6	0	..	..	8	0	3	33
120	11	18						
140	22	27	20	0				
150	..	..	..	..	..	..	3	66
160	23	48	20	15				
180	22	77	20	20				
200	7	100	20	70	2	0	1	100
220	..	..	20	85				
230	..	..	5	100	8	25		
250	..	..	..	..	8	62	1	100
275	..	..	..	..	5	80		
300	..	..	..	..	4	75		
350	..	..	..	..	3	100		

* One per cent dye in 5% dextrose solution.

Repeated Intravenous Injections. Six rabbits were injected daily by vein with from 25 to 50 mg. per kg. Congo red for 7 to 14 days. No ill-effects were observed in any of the animals, nor was there any loss of body weight. Four pigeons were given 4 daily intravenous injections of 50 mg. per kg. each, or a total of 200 mg. per kg. of pigeon, without demonstrable effects. Three of the rabbits used received 50 mg. per kg., for 14 days, or a total of 700 mg. per kg. This would correspond to a total of 42 gm. for a 60-kilo man, which is much greater than the doses proposed thus far. Accordingly, there are few therapeutic agents which have such a large margin of safety as Congo red used intravenously. However, large single and repeated small doses cause marked disturbances of the circulation which may result in death.

Cause of Death from Intravenous Injections. The cause of death from Congo red used intravenously was studied in 10 rabbits and 13 cats. The rabbits were anesthetized with 30 mg. pentobarbital per kg. intraperitoneally, and the cats, with 1.5 gm. urethane per kg. gastrically. Blood pressure was recorded from a mercury manometer joined to a carotid artery; respiration was recorded with a

tambour attached to the side arm of a tracheal cannula, and venous pressure, from a long glass cannula passed down the jugular vein and into the right auricle. Oncometers were placed on the heart, leg, liver and intestine for volume records for determination of vascular changes. Most of the animals were atropinized and curarized. Fatal doses of Congo red were injected intravenously in single and repeated small doses in different animals.

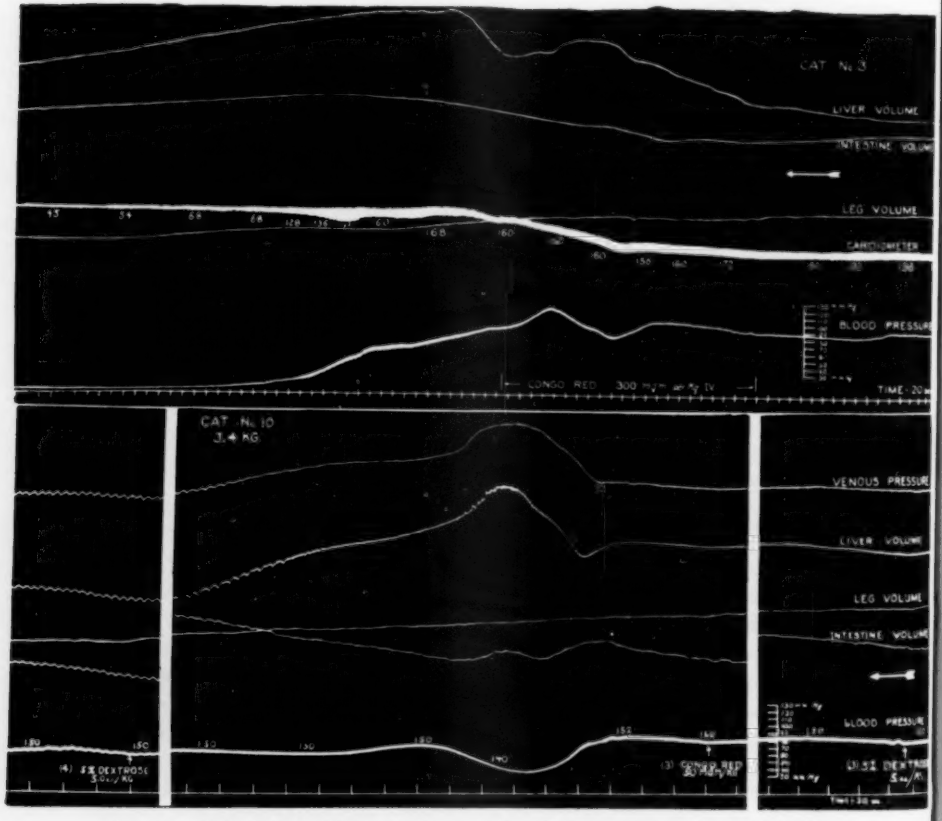

FIG. 1.—Circulatory effects of Congo red. Upper record: single fatal dose: Cat 3 (2.5 kg.); 1.5 gm. urethane gastrically; curarized and atropinized; 300 mg. per kg. Congo red into saphenous vein. Lower record: repeated small doses: Cat 10 (3.4 kg.); 1.5 gm. urethane gastrically; atropinized and curarized; showing third and fourth injections of 5 cc. 5% dextrose solution and third injection of 50 mg. Congo red, each per kg., into saphenous vein.

Single Fatal Doses (Fig. 1). Doses of 350 to 400 mg. per kg. injected at once caused an initial rise of blood pressure, with an increase or a decrease in pulse rate. Before the injection was completed, the blood pressure began to fall gradually and continued

to the zero level. As the pressure approached zero, the pulse slowed down and finally ventricular contractions stopped altogether. Respiration was not changed either as to rate or depth, until the blood pressure reached shock level. At this point, alternate periods of apnea and hypernea often occurred. Respiration never stopped completely until the blood pressure had fallen to the zero level.

During the phase of rising blood pressure, the liver, intestine and leg all showed some increases in volume. The venous pressure rose slightly and the heart dilated, usually with a coincident increase in amplitude of contractions. As the blood pressure began to fall the venous pressure suddenly rose, the liver and intestine continued to increase in volume, but the leg diminished in size. The amplitude of the cardiac contractions became smaller, with a marked diastolic tendency. When the blood pressure fell below the shock level, the liver and intestine usually decreased slightly in volume and the venous pressure fell.

These phenomena are consistent with circulatory collapse, probably due to direct cardiac depression by the dye. As a result, the blood is dammed back in the venous system, thus causing passive congestion of the lungs, liver and intestines. The leg becomes passively constricted because of diminished cardiac output of blood into the periphery. These phenomena and duration of life are not affected by artificial respiration begun before the injection and continued throughout the experiment. Atropine has no effect on the terminal slowing of the heart, thus indicating that the depressant action of the dye is direct on the cardiac muscle and not of reflex vagus origin. When the blood pressure has fallen to the shock level, epinephrine, in large doses, produces a small and typical, though fleeting, rise in blood pressure, which is further evidence of the cardiac depression. That death from single fatal doses of Congo red is not due to the volume of fluid injected was shown by the fact that the injection of equal volumes of isotonic dextrose solution produced only slight rises in pressure. The results with such an "inert" solution resemble closely those of the initial action of Congo red. That is, with the slight arterial pressor effect the venous pressure rises slightly and there are slight increases in size of the leg, liver and intestines, with a slight diastolic distention of the heart. Complete recovery from Congo red occurs in 15 to 20 minutes. The initial results are plainly fluid-volume effects plus some colloid effects which, however, are not comparable with those of blood transfusion, or of acacia under favorable conditions.

Repeated Small Doses. Up to 4 successive intravenous injections of 50-mg. doses of Congo red per kg. were given. These were alternated with injections of equal volumes of 5% dextrose (or 6% acacia) solution, in order to compare the effects of the colloidal dye with a comparatively inert crystalloid and a colloid, as controls. Injection of the first dose of 50 mg. Congo red produced no greater

effect than the control solutions, but the second or third injection produced a profound, though fleeting, depression of the circulation (Fig. 1). This depression occurred when a total of 100 to 150 mg. per kg. of the dye had been injected, an amount close to a fatal dose. This depression lasted about 5 minutes, and the organ changes were similar in all respects to those from a single large fatal dose. After 4 injections of Congo red, or a total of 200 mg. per kg., had been given, further injections of the dye had practically no more effect than dextrose or acacia alone. However, by this time, the blood pressure had fallen steadily, and the animal died finally from cardiac paralysis as from a single fatal dose. In view of this apparent cardiac poisoning in the intact mammal, it was interesting to observe the effects of the dye directly on cardiac muscle of perfused and excised strips.

Effects on Cardiac Muscle. Experiments were made with perfused turtle and frog hearts and excised strips of rabbit auricle. Six turtle hearts were perfused *in situ* according to Greene's method, using the dye in turtle heart—Ringer's solution.[10] The output was recorded by an automatic bucket recorder. Contractions were recorded with a lever attached to the frenulum at the apex of the ventricle. After a satisfactory control record, Congo red in concentrations of from 1 to 40,000 to 1 to 1000 was added to the perfusion fluid.

All hearts showed a prompt systolic tendency (Fig. 2), the contractions became smaller, and the flow decreased or stopped. With higher concentrations, the ventricles stopped in systole, but the auricles continued to beat feebly. After repeated perfusion of the dye, the heart became less sensitive and, in some cases, responded only to high concentrations. The marked systolic contraction was partly relieved by perfusion with quinidine or excess potassium, but atropine had no effect, thus indicating that the systolic action was the result of a stimulation of this cardiac muscle.

Six frog ventricles were perfused according to Straub's method. After a satisfactory control period, perfusion fluid containing Congo red in concentrations of from 1 to 20,000 to 1 to 200 in frog Ringer's solution was added to the cannula. Under these conditions, the frog ventricles responded quite differently from the turtle hearts, for in only 2 ventricles was systolic standstill obtained. The typical response may be seen in Figure 2, which shows a transient period of stimulation, during which the amplitude of contractions was increased, followed by a progressively increasing depression, the heart stopping in diastole. The entire course of events required 15 to 35 minutes, depending on the concentration of Congo red. In 2 cases, the ventricle stopped in systole, but after a few minutes relaxed and remained dilated. The rate was usually not affected until just before stoppage, when the contractions slowed down rapidly.

Three experiments were made with excised strips of rabbit auricle. The rabbits were killed by bleeding, and the hearts removed immediately after death. Strips of the auricle were attached to a light heart lever and immersed in a bath containing 10% blood in oxygenated Locke's solution. After a control period, Congo red in a concentration of 1 to 1000 was added. Within a few minutes the contractions became smaller and the general tone of the strip increased. The rate was practically unchanged (Fig. 2). When the Congo red solution was replaced with fresh Locke's solution, the strip recovered partially from the stimulation. As with turtle hearts, repeated application of Congo red to frog ventricles produced a refractory state so that very high concentrations of the dye were necessary to produce demonstrable effects.

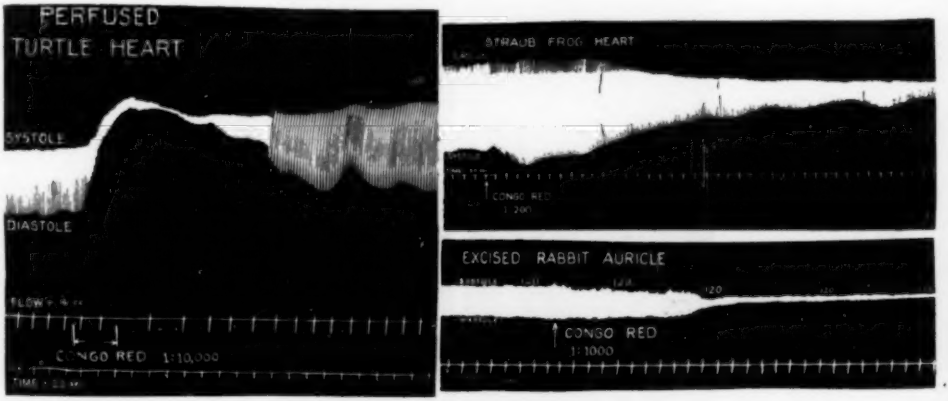

FIG. 2.—Effects of Congo red on perfused turtle heart and isolated frog ventricle and rabbit auricle.

The results obtained on isolated amphibian and mammalian cardiac muscles indicate that Congo red tends to stimulate this type of muscle. This seems to be true for the more stable turtle and rabbit hearts than for the less stable frog hearts, although the latter showed evidences of stimulation in the majority even though sometimes fleeting. Although a digitaloid action has been claimed for some dyes, and the results obtained by us resemble such action, our analysis was not sufficient to justify comparisons along this line. The stimulation of the isolated heart does not, of course, agree with the depression of the heart *in situ*, but the usage of Congo red was not comparable. That is, the dye was used in saline solutions on the isolated heart and such solutions lose their colloidal properties, whereas in the intact circulation the colloidal properties are probably preserved. While the relationship of the physical state of the dye to cardiac function is not understood, this should not be overlooked in determining the fundamental nature of the pharmaco-

dynamic action of the dye.* Unfortunately, circumstances did not permit us to continue with this part of the work at this time. The tonifying action on cardiac muscle is worthy of further study as it was found also on smooth muscles.

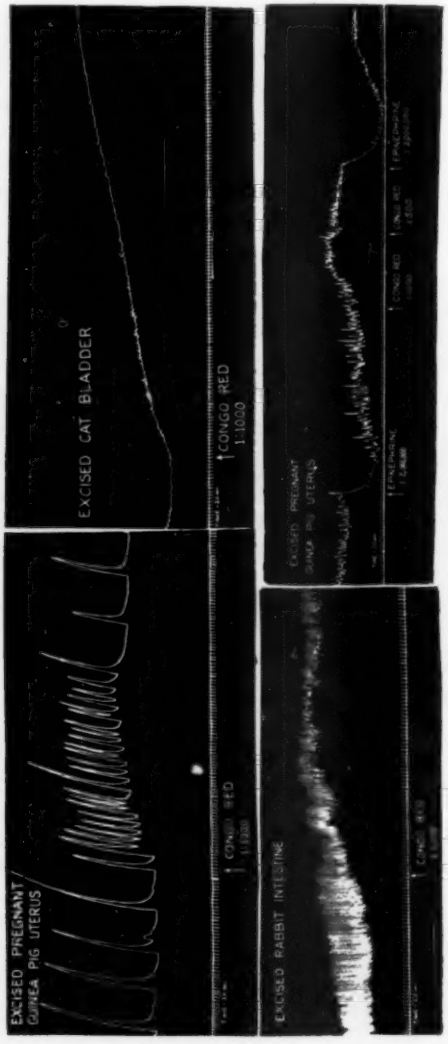

FIG. 3.—Congo red on excised organs.

Excised Smooth Muscles. Congo red has been reported to produce a tonifying action on smooth muscle, particularly on excised intestine.[2,12] We have tested the effects of the dye on other smooth muscles and confirmed that the stimulation is general, and direct

on the muscle. Results were obtained with uterus, intestine and bladder of cats, guinea pigs and rabbits. Oxygenated Tyrode's solution was used throughout. From 17 to 26 tests were made on all organs obtained from at least 3 different animals of each species. The following concentrations of the dye were used on the different organs: bladder, 1 to 1000 to 1 to 500; pregnant and non-pregnant uterus, 1 to 2000 to 1 to 250, and intestine, 1 to 5000 to 1 to 500. The reactions of all these organ strips were characterized by an increase in tone and a decrease in amplitude of contractions. On the whole, Congo red in 5% dextrose solution caused more pronounced effects than in Tyrode's solution. The typical effects of the following autonomic drugs were produced on all organs after treatment of the organ with, or in the presence of, Congo red: barium, epinephrine and nitrite. Acetylcholine and nicotine were still effective on intestine. The reactions of intestines to post-pituitary solution were often, though not consistently, decreased after the addition of the dye to the organ. Using the dye in whole plasma, or in 10% blood in Tyrode's solution, produced smaller stimulant reactions in the organs. Previous atropinization and nicotinization of the bladder and intestine and ergotoxinization of augmentor types of uteri did not prevent the tonifying action of the dye. Illustrations of typical reactions of the different organs to the dye and to autonomic drugs are presented in Figure 3.

According to the results obtained, Congo red is a direct smooth muscle stimulant for isolated intestinal and urogenital organs, independently of innervation, but in the presence of blood colloid elements this stimulation is appreciably reduced. The typical reactions to autonomic muscle-nerve poisons are preserved in the dyed organs. Our results with drugs on excised intestinal muscle confirm those of Ishigami.[4] The results of several investigators leave doubt that Congo red can excite the motor activity of cardiac and smooth muscles, but how this excitation is produced is not understood. Whether the dye acts similarly on skeletal muscle is not known, although Ishigami claims that the irritability of skeletal muscle and nerve of frogs is not affected. However, it is well known that the dye can protect skeletal muscle and nerve from the paralytic action of curare. The protective action of Congo red can be extended to a variety of cellular and tissue functions, a phenomenon to be described in another paper.

Conclusions. 1. The intravenous fatal dose of Congo red in pigeons, rats, rabbits and cats varies from about 150 to 250 mg. per kg. for over 60% of the animals. The comparatively small doses used in therapeutic and diagnostic practices indicate a wide margin of safety in the use of the dye intravenously.

2. The toxic symptoms are characterized by general depression and collapse. The dye is less toxic in dextrose than in saline

solutions. The cause of death from Congo red is circulatory collapse, as a result of direct cardiac depression.

3. Cardiac muscles of the perfused turtle heart and frog ventricle and excised rabbit auricle are generally directly stimulated by Congo red as indicated by an increase in tone, and stoppage of the heart in systole; frog ventricle showing variations in reaction.

4. Congo red stimulates directly the smooth muscles in isolated bladder, pregnant and non-pregnant uterus, and intestine, by a direct action on the smooth muscle. Reactions of these organs to autonomic drugs are not changed by the dye.

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CONGO RED: ABSORPTION, DISTRIBUTION AND SOJOURN IN BLOOD.

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Congo red has been used intramuscularly and intraperitoneally in therapeutics without substantial proof of adequate absorption by these routes.[4,9] Since many systemic effects of the dye probably depend on an adequate concentration in the blood, information on the content and sojourn of the dye in the circulation is of utmost importance, including knowledge of its distribution in the tissues and fate in the body. This paper presents data obtained from animals bearing on these questions.

Estimation of Congo Red in Blood and Tissues. The concentration of Congo red in plasma can be determined by direct comparison with solutions of the dye of known strength, but this method is unreliable for blood, or in the presence of hemolysis and unsatisfactory for tissues. Some time was spent in working out a procedure which could be applied to blood and tissues. Precipitation of the proteins with trichloracetic acid, tungstate, heat and so on was tried, but discarded because the Congo red was removed with the cellular constituents. Preliminary digestion of the protein material with pepsin and pancreatin did not result in a satisfactory recovery

of the dye. Extracting with alcohol[3] gave better results, but with some tissues, particularly liver, recovery was poor. Extraction with acetone, according to Taran,[7] yielded the best results.

The following procedure was finally adopted: The sample of tissue was cut into small pieces and ground in a mortar with a small amount of sand and water until an even mash was produced. Two volumes of acetone were mixed with 1 volume of tissue mash, shaken, and allowed to stand for 1 to 2 minutes. The mixture was then filtered through medium filter paper. Such treatment gave a clear colorless filtrate with all blank (undyed) tissues, except liver which sometimes gave a slight yellowish color. Bile and urine and pigeon blood also gave yellowish filtrates, which concealed low concentrations of Congo red. The acetone extract was compared directly with permanent known solutions of the dye as standards, which were diluted so that results could be read directly. The method was checked with Congo red added to blood and tissues in concentrations of from 1 to 1000 to 1 to 100,000. The total dye recovered was from 95 to 100%, from all concentrations to 1 to 50,000. With liver and urine, recovery at this concentration was only about 50%. About 75% Congo red could be recovered from blood and most tissues containing added concentrations of 1 to 100,000.

Absorption and Sojourn in Blood. The systemic absorption of Congo red after intramuscular, intravenous and intraperitoneal injections was determined by the level of the dye in the bloods of rabbits and pigeons at different periods following the administration of 1% Congo red in 5% dextrose solution. Blood was withdrawn by cardiac puncture at intervals of 4 minutes, 1 hour and 4, 8, 12 and 24 hours, after injection. It was put directly into 2 volumes of acetone, and the Congo red determined according to the method outlined.

TABLE 1.—AVERAGE CONGO RED CONTENT OF BLOOD ACCORDING TO DIFFERENT METHODS OF ADMINISTRATION.

	Pigeons (75 mg. per kg.).			Rabbits (100 mg. per kg.).		
Time.	Intramuscular, mg. %.	Intraperitoneal, mg. %.	Intravenous, mg. %.	Intramuscular, mg. %.	Intraperitoneal, mg. %.	Intravenous, mg. %.
4 min.	0.0	6.25	125.0	0.0	0.0	160.0
1 hour	0.3	7.40	55.5	1.6	16.0	128.0
4 hours	*	4.70	17.9	2.1	25.0	69.0
8 hours	0.0	3.20	8.9	2.0	22.0	42.0
12 hours	0.0	1.80	3.0	1.3	13.0	16.0
24 hours	0.0	0.85	0.6	1.0	1.0	0.2

The results obtained on 9 rabbits, injected with 100 mg. per kg. Congo red, 3 each intramuscularly, intraperitoneally and intravenously, are presented in Table 1. The concentrations after intravenous injections agree closely wish those obtained in man by Bennhold,[1] who reported a 20% removal of the dye during the first hour; only a trace remaining at the end of 24 hours. The intramuscular and intraperitoneal injections gave poor results, since the peak of absorption in each group occurred in about 4 hours, and the blood concentration after intraperitoneal injections was only one-

third that obtained after the intravenous, in a corresponding period. At no time did intramuscular administration result in the magnitude of systemic absorption achieved with intravenous and intraperitoneal injections; it was only about one-tenth to one-thirtieth the content at certain intervals.

The results on 18 pigeons each injected with 75 mg. Congo red per kg. were similar to those on rabbits; 3 groups of 6 pigeons each were injected intramuscularly, intraperitoneally and intravenously. About the only difference from rabbits was a more rapid disappearance of the dye from the blood, nearly 50% being removed at the end of the 1 hour after intravenous injection. For the same reason, the intramuscular and intraperitoneal injections never gave blood concentrations equal to those of intravenous injections.

The poor results on systemic absorption of Congo red obtained with administrations other than intravenous are not surprising considering the physical properties of the dye. For it is well known that colloidal substances are poorly absorbed from the muscles and the peritoneum. Obviously, therefore, when the systemic actions of Congo red are dependent upon a high level of dye in the circulation, the only acceptable method of administering it is the intravenous. Furthermore, where a prolonged action is desired, as in pernicious anemia, experimental intoxications, and infections, the dye must be administered repeatedly in order to insure a continuous systemic action. According to results in animals treated with high and extra therapeutic doses, the dye content of the blood approaches a level of inefficiency by the end of 12 hours and is practically absent at the end of 24 hours, regardless of the method of administration. Smaller and therapeutic doses would possibly require injections as often as every 4 hours, but this suggestion should be tested in case of human medication.

Distribution of Congo Red in Tissues. It has been suggested that Congo red is removed from blood chiefly by the reticulo-endothelial cells and the rate of removal is a measure of the functional efficiency of this system.[2,6,10] If this hypothesis is correct, Congo red should be distributed according to the richness of organs in reticulo-endothelial cells. The results obtained by me do not sustain this. On the contrary, the Congo red is distributed fairly evenly in the extracellular tissue fluids of the body.

Ten rabbits and 4 cats were injected intravenously with 1% Congo red in 5% dextrose solution, using doses of from 50 to 450 mg. per kg. Tissues were removed 1, 24 and 72 hours later. No effort was made to wash out all the blood. The results obtained are shown in Table 2, grouped according to time of tissue removal after injection, so that animals with a high blood content of the dye could be compared with those with a low blood content.

It is seen that 1 hour after ingestion of doses from 50 to 450 mg. per kg. the Congo red was chiefly in the blood and those organs

with rich capillary beds. Apparently, anesthesia and nerve paralysis had no influence on the distribution of the dye, except for quantitative differences due to the different doses used. The cats had been used for toxicity studies of the dye and were urethanized, atropinized and curarized.[5] The high blood content was not surprising in view of the colloidal nature of the dye. Interestingly, the lungs contained the highest concentration of all the tissues examined. This was particularly true of cats receiving the fatal doses. Kidney, liver and pancreas were next highest, and then came the heart and spleen. Striated muscle and brain invariably contained the least amount of dye. Bile from the gall bladder contained about as much as liver, while urine contained an undetermined amount despite the high renal concentration of the dye.

TABLE 2.—DISTRIBUTION OF CONGO RED IN TISSUES OF RABBITS AND CATS.

Time after injection	One hour.		Twenty-four hours.			Seventy-two hours.
Total dye injected, mg. per kg.	50	450*	50	100	700†	275
Number of animals	2	4	2	2	2	2
	Mg. %.	Mg. %.	Mg. %.	Mg. %.	Mg. %.	Mg. %.
Blood	43.5	568.0	0.00	0.5	0.57	0.57
Brain	0.48	4.9	0.00	0.0	0.30	0.55
Muscle	0.37	3.8	0.00	0.41	0.36	1.77
Skin	1.6	..	0.56	..	3.2	2.6
Heart	18.4	..	0.22	..	3.1	5.38
Spleen	2.9	279.0	1.72	..	7.9	91.0
Pancreas	..	210.0				
Liver	18.2	197.0	2.5	15.6	41.2	62.7
Lung	23.5	434.0	1.9	5.7	15.7	27.2
Kidney	22.9	228.0	28.6	49.9	105.7	104.8
Bile	21.6	..	146.0	..	162.0	59.5
Urine	(+)	(−)	(−)	..	3.1	(−)

* This group consisted of cats, anesthetized with 1.5 gm. urethane per kg.; all other animals were rabbits.

† Daily dose of 50 mg. per kg. for 14 days.

The blood was nearly free of the dye 24 hours after injection of doses of 50 to 100 mg. per kg. in 4 rabbits and 50 mg. daily for 14 days (total 700 mg. per kg) in 2 other rabbits. The tissues gave values which varied only quantitatively. The concentration of the dye in the tissues could not be attributed to the blood content of the dye, since the blood was practically free of the dye. Blood, brain and striated muscle of all animals contained about equal, although the lowest, concentrations of dye. Skin and heart muscle contained appreciably larger amounts, while spleen, lung, liver and kidney, in this order, contained increasing amounts. The kidneys always contained twice as much as any other tissue. Bile from the gall bladder generally contained very large quantities, while urine contained only small amounts of the dye, if any. The comparative absence of the dye in urine was surprising in view of the high renal

content. Since the Congo red was not readily released from the kidneys, these organs presumably possess a selective retention for it.

The high retention of the dye in the kidneys was evident also in the 2 rabbits which had been given 275 mg. per kg. At this time, the concentration in the bile had fallen to about one-third that at the end of 24 hours. While the biliary channels are the main paths for excretion of the dye, the kidneys, by contrast, held relatively much more. The remaining tissues contained about the same amounts as at 24 hours. For instance, the blood content was practically the same. In other words, there appears to be a delayed removal from the system after 24 hours of sojourn in the body.

Many of the tissues were examined histologically in an attempt to locate the Congo red in the cells, but only in the kidneys was it possible to identify the dye. In these organs, the dye was present chiefly in the cells of the tubules, where it had a granular appearance. The entire protoplasm and extracellular spaces were definitely stained a diffuse red color. Most of the glomeruli remained uncolored. The nuclei of the cells were comparatively free of the dye.

It is clear from these results that, even as late as 72 hours after intravenous injection, when the greater part of the dye has long been removed from the blood stream, Congo red is distributed systemically without demonstrable relationship to the reticuloendothelial system. Accordingly, the use of Congo red as a functional test for this system is based on a false hypothesis. With the exception of the high concentration in the kidney tubules, Congo red tends to be distributed evenly in those organs having a high extracellular tissue fluid. The organs, which Wallace and Brodie[8] reported taking up large quantities of iodide and thiocyanate, are the same organs which take up large quantities of Congo red. However, the data obtained by me would seem to indicate that the Congo red in the liver, spleen, lungs, kidneys, skin and so on is partially bound, physically or chemically, by some cellular or noncellular constituent, otherwise its concentration would remain in equilibrium with that of the blood. Proteins are apparently not concerned, since the dye escapes fairly readily from the blood. It is conceivable that tissue fluid or lymph may contain some substance like amyloid, or its precursor, which has a strong affinity for Congo red, and that, in the condition known as amyloidosis, this substance is merely increased. Further study of this phenomenon was not attempted at this time.

Conclusions. 1. Intramuscular and intraperitoneal injections of Congo red in pigeons and rabbits failed to produce concentrations of the dye in the blood comparable to intravenous injections.

2. Injected intravenously, Congo red disappears from the blood stream at a constant rate, only traces of the dye remaining at the end of 24 and 72 hours, even after large doses.

3. After disappearance from the circulation, most of the Congo red is distributed to those organs possessing large amounts of extracellular tissue fluid, and is presumably loosely bound in some way to some substance or structure in tissue fluid.

4. The kidneys of cats and rabbits possess a rather high selective retention for Congo red, but the biliary passages are the main channels for excretion of the dye.

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CONGO RED: HEMATOLOGIC ACTIONS.

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Some of the most interesting though controversial effects of Congo red are those on blood. Despite many clinical reports of its usefulness in treatment of pernicious anemia and hemorrhages, there have been few controlled studies of its effects on hemolysis, cell counts, suspension stability, coagulation and bleeding time.

Antihemolytic Action. That Congo red may, under certain conditions, cause remissions in pernicious anemia supports the opinion of Dock,[1] among others, that this blood disease is fundamentally a hemolytic anemia. A protective action of the dye for the fragile erythrocytes, *i.e.*, an antihemolytic action, might be the basis of the beneficial effects of Congo red in pernicious anemia. The following experiments were made to test the possible antihemolytic actions of this colloidal dye in various *in vitro* hemolytic systems. Whole human blood from healthy males was added to each hemolytic system, the final concentration of red cells being 1%. Changes in hemolysis were determined by counting the cells in a hemocytometer chamber. The results were recorded in per cent hemolysis of the original concentration of blood. The results obtained are presented as curves in Figure 1.

Hypotonic Sodium Chloride Solution. Tests of fragility in hypotonic sodium chloride solution containing the dye were made as follows: 2.7 cc. of sodium chloride solution with salt concentrations of from 0.5 to 0.26% were mixed with 0.3 cc. Congo red solution to make final concentrations of the dye 1 to 4000, 1 to 2000 and

1 to 1000. As controls, the same dilutions of sodium chloride were mixed with 0.3 cc. 5% dextrose solution. After adding the blood, the tubes were shaken and allowed to stand in an incubator at 37° C. for 2 hours. The results of a typical experiment are shown

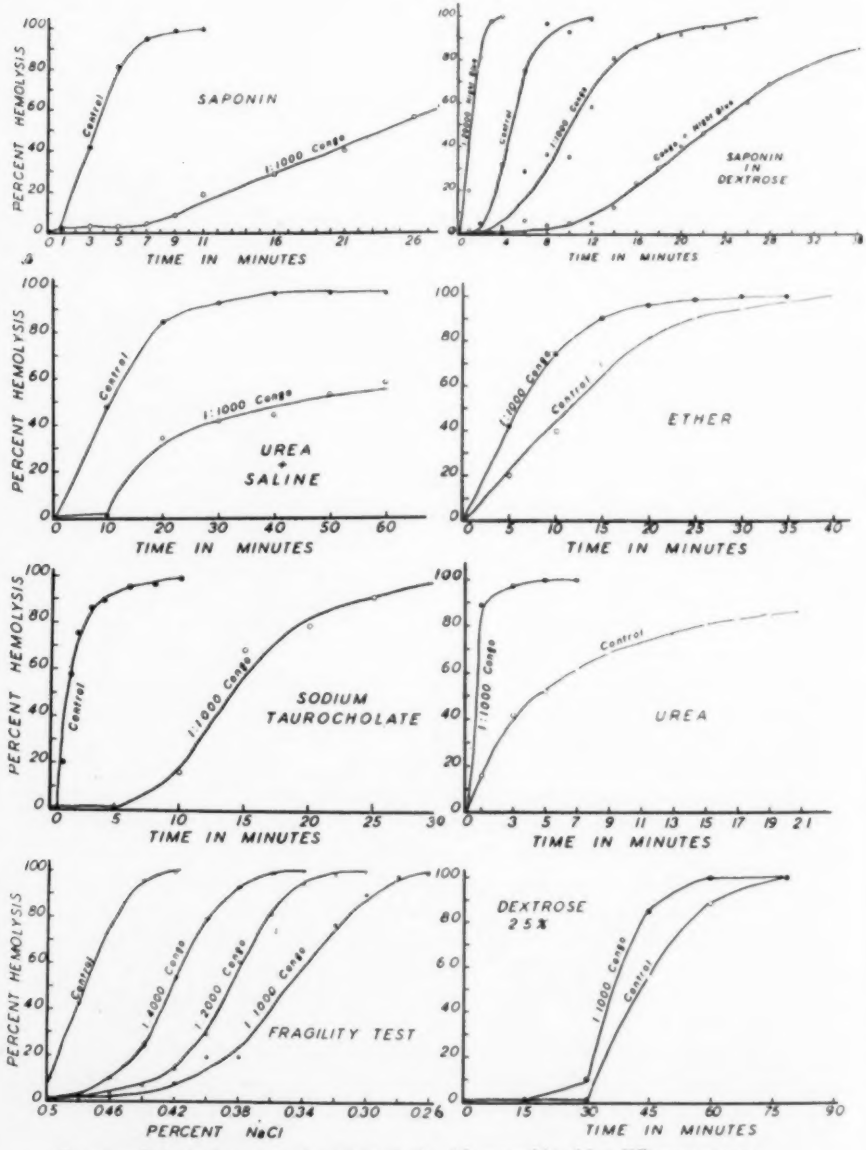

FIG. 1.—Effect of congo red on hemolysis of human blood by different agents.

in the left-hand corner of Figure 1, in which per cent hemolysis is plotted against concentration of salt. A protective action of the Congo red is clearly evident. Whereas, in the control, 50% hemolysis occurred in 0.48% sodium chloride, not so in Congo red. Definitely lower dilutions, *i. e.*, 0.42, 0.39 and 0.35%, were required to produce the same degree of hemolysis when the dye was present in concentrations of 1 to 4000, 1 to 2000 and 1 to 1000, respectively. Essentially the same results were obtained with 3 other samples of blood.

That the degree of inhibition was directly dependent on the concentration of the dye at the time hemolysis was taking place was shown in the following experiment: Whole blood was mixed with Congo red 1 to 1000, and the mixture was allowed to stand for 2 hours. At the end of this time, the resistance of this mixture to hypotonic saline solution was compared with that of a control sample of blood and found to be identical.

Isotonic Dextrose Solution. Since blood mixed with isotonic dextrose solution is rather promptly, though partially, hemolyzed, it was not feasible to test the effect of Congo red on the resistance of red cells to varying hypotonic strengths of this sugar. Instead, the speed of hemolysis in dextrose solutions was determined in the presence and absence of Congo red. One test tube was filled with 2.5% dextrose solution and sufficient Congo red added to make a concentration of 1 to 1000; another tube was filled with 2.5% dextrose solution plus 5% dextrose equal to the volume of dye in the first tube. Blood was added, and both tubes were shaken and put in an incubator at 37° C. The cells remaining in each tube were counted every 5 minutes, and per cent hemolysis plotted against time. The averages of 3 such experiments are shown in the right hand corner of Figure 1. It is seen that Congo red caused a slight, but definite, increase in speed of hemolysis as compared with the control.

Ether. Ether, 7% strength, in 0.9% sodium chloride solution was used as a hemolyzing agent. To one test tube was added ether-saline solution plus Congo red to a final concentration of 1 to 1000, and to another tube ether-saline solution plus 5% dextrose. After the addition of blood, both tubes were stoppered and allowed to stand at room temperature. Cell counts were made every 5 minutes. The averages of 3 experiments, shown in the right upper segment of Figure 1, were similar to those with dextrose, and leave no doubt of a definite increase in speed of hemolysis caused by the dye, as compared with the control.

Hypertonic Urea Solution. As is well known, urea, even in "hypertonic" strength, causes a rapid hemolysis of red cells. A solution of 20% urea in distilled water was used, and 2.7 cc. of this solution was made up to 3 cc. with sufficient Congo red to make a concentration of 1 to 1000, and of 5% dextrose solution for the con-

trols. Blood was added to each tube and red cell counts were made every few minutes. The curves in Figure 1, which show averages of 3 experiments, leave no doubt that Congo red caused rapid and complete hemolysis, while the control untreated blood required about 20 minutes for complete hemolysis. Therefore, the results were similar to, but more striking than, those with dextrose and ether.

Urea in Saline Solution. Since the results with hypotonic saline solution showed a striking protective action of Congo red, but in solutions of dextrose, ether and urea, the effects were just the reverse, it was interesting to consider if the sodium chloride played a part in the protective action. Figure 1 shows the average results of 3 experiments in which 0.5% sodium chloride was added to the 20% solution of urea. Tubes of this solution were prepared without and with Congo red, 1 to 1000, blood was added, both tubes were shaken and then allowed to stand in an incubator at 37° C. Cell counts were made every 10 minutes. The control tube without the dye showed complete hemolysis in about 40 minutes, while tubes containing Congo red, only about 50% hemolysis at the end of 1 hour. Thus, the presence of salt mediated a protective action of the Congo red against hemolysis by urea, and the same was true for taurocholate and saponin.

Sodium Taurocholate in Saline Solution. Sodium taurocholate, 1 to 1000, was tried in 0.9% sodium chloride solution. Hemolysis of red cells in the absence and presence of Congo red, 1 to 1000, in this solution, was observed in 3 experiments. The average results are shown in Figure 1. In the control tube, hemolysis was complete in 5 minutes, while in the presence of Congo red it was not complete until about 30 minutes.

Saponin in Saline and Dextrose Solutions. Saponin, 1 to 20,000, in normal saline solution was tried. Congo red, 1 to 1000, was added to the saponin solution, and as a control, an equal volume of 5% dextrose solution was used. Blood was added, and cell counts were made every few minutes. The averages of 3 experiments in Figure 1 show that Congo red produced a striking inhibitory effect. The cells in the control tube were completely hemolyzed in 7 to 8 minutes, while, in the presence of Congo red, only about 60% of the cells were destroyed in 26 minutes.

A further test of the protective action of Congo red against saponin was made with solutions of the dye in dextrose solution, instead of saline solutions. Saponin, 1 to 7000, in 5% dextrose solution was used and the speed of hemolysis determined in the absence and presence of Congo red, 1 to 1000. The averages of 3 experiments in Figure 1 show that Congo red delayed hemolysis about 25 minutes, while the control tube showed complete hemolysis in 12 minutes.

Nature of the Antihemolytic Mechanism. Since the protective action of Congo red against saponin was enhanced by the presence of salt, experiments were made to determine whether this action could be due to some change produced in the physical state of the colloidal dye. For this purpose, Night Blue, an electropositive dye, was used. This dye was added to the same saponin-dextrose system in a concentration of 1 to 20,000 with the result that the speed of hemolysis was increased (Fig. 1). However, when the Night Blue was combined with the Congo red, a striking protection against saponin-hemolysis was produced (Fig. 1). This result can only be explained by some change in the physical state of the Congo red, which is precipitated by Night Blue as well as by salt. Accordingly, the protective action of Congo red may be due to the formation of a protective film on the surface of the red cells by the precipitated Congo red. Precipitation of this electronegative, emulsoid dye is not as efficient in the presence of sodium chloride as of Night Blue. Therefore, Congo red, in saline solutions, would be expected to give variable, or incomplete protection, as indeed was the case with the different agents tried (Fig. 1).

Congo red shows protection against hemolysis with such a large variety of agents that it appears probable the protection is not due to any specific action on the individual hemolytic agents. In hypotonic sodium chloride solution, the protection could be a salting (precipitating) action on the dye and explained by some film effect on the cells. Therefore, it would be reasonable to expect that the same mechanism would operate in all cases where sodium chloride was present, and this was found to be true generally. With saponin and some of the other agents, the possibility should not be overlooked that the toxic substance may be adsorbed on the surfaces of the dye aggregates and thus might prevent, or render inefficient, a contact with the red cells. However, protection against the hemolysis of saponin in the intact organism could not be demonstrated, but the experimental procedure was not satisfactory. Studies of changes in circulating blood may now be described.

Effects on Blood of Intact Animals. A total of 21 rabbits and 1 cat were used. Congo red was injected in doses of from 10 to 100 mg. per kg. intravenously, as single doses and as daily doses for 1 and 2 weeks. Following the single doses, blood was examined 1 hour, and 3 and 24 hours later, and after repeated doses, 24 hours after the last injection. All procedures for examination of the blood were carried out according to the methods described by Todd and Sanford.[5] Except for platelet and reticulocyte counts, all bloods were obtained by cardiac puncture. As anticoagulant for the blood, potassium oxalate was used, 10 mg. in 1 cc. of blood. The following results were obtained.

Hemoglobin. This was determined with a Sahli hemoglobinometer. The greatest deviation observed from normal, in any one

animal, was a decrease of 7%, which occurred 24 hours after a single injection of 100 mg. per kg. of the dye. Rabbits receiving 50 mg. per kg. daily for 2 weeks showed no demonstrable changes.

Packed Cell Volume. This also showed little or no change. As with hemoglobin, the greatest change occurred in those rabbits receiving single injections of 100 mg. per kg., and even then there was only an average decrease of 4%.

Red Cell Counts. These followed closely the results on hemoglobin and packed cell volume; no significant changes occurred after single and repeated injections of 25 and 50 mg. per kg. of Congo red. However, 24 hours following 100 mg. per kg., the average count in 2 rabbits fell from 4.4 million to 3.5 million red cells per c.mm. The small decreases in hemoglobin and red cells after large doses of Congo red would be consistent with either destruction or dilution of the blood, but analysis of the phenomenon was not made.

Platelets and Reticulocytes. These elements were determined by the so-called wet method, using brilliant cresyl blue and sodium citrate, the blood being obtained by puncturing a small ear vein. Immediately and for several hours following the injection of 100 mg. per kg. of the dye, the platelets and reticulocytes could not be counted because of agglutination of the red cells about the platelets. The cells were only loosely clumped, since dry smears failed to show this phenomenon. However, the agglutination was indicative of some change in the cell surfaces. Platelet counts, after all doses of Congo red, showed both increases and decreases, which did not average more than 60,000 per c.mm., and were well within the normal range. Reticulocytes showed no change, except in rabbits given 50 mg. per kg. daily for 2 weeks. These continued doses caused a slight reticulocytosis of about 0.7%, probably without significance.

Leukocytes. The counts after 25 mg. per kg. of Congo red, in single and repeated doses, showed no changes. Single injections of 50 or 100 mg., however, increased the white count 4000 to 9000 cells per c.mm. The peak of leukocytosis occurred in 1 to 2 hours, with return to a normal white cell count 20 hours later. The leukocytosis was marked chiefly by an absolute increase in the number of neutrophils.

Sedimentation Rate. This was determined in Cutler tubes of 1-cc. capacity. Because of the normally slow sedimentation rate of rabbit blood, observations had to be made over a period of 3 hours instead of 1 hour, the usual period for other bloods. Single injections of 25 mg. per kg. of the dye increased the sedimentation rate about 80%, while 100 mg. per kg. increased it about 350%. The increase in sedimentation lasted for 48 hours, at least, after a single injection of the Congo red. Hemagglutination, or blood dilution, might be responsible for this change, but it was not studied further.

Blood Coagulation and Bleeding Times. The literature on the effect of Congo red on the clotting time of blood has been reviewed recently by Taliaferro and Haag,[4] and also by an anonymous writer,[3] therefore, it is omitted here. Briefly, most of the reports have been clinical, and unfortunately, not well controlled. The results claimed have been rather striking and to the effect that both phenomena are shortened, thus providing a basis for the alleged hemostatic action of Congo red. The claims seemed worthy of confirmation or refutation and the attempt was made on 21 healthy rabbits.

Bleeding time was determined by transecting a small vein in an ear and noting the time required for the blood flow to stop. As nearly as possible, a vein of the same size was used each time. Coagulation was determined on blood drawn into a syringe directly from the heart and expelled into a small clean test tube. The tube was tipped every 15 to 30 seconds until it could be completely inverted without flow of blood. After suitable control observations on each animal, Congo red was injected intravenously in doses of 10 to 100 mg. per kg. and the coagulation and bleeding times were determined 5 minutes, 1, 3 and 24 hours later. Some rabbits were injected with 25 and 50 mg. per kg. of the Congo red for 1 and 2 weeks, the coagulation time being determined 24 hours after the last injection. Table 1 presents a summary of the results, which were essentially negative.

TABLE 1.—BLOOD COAGULATION AND BLEEDING TIMES IN RABBITS INJECTED WITH CONGO RED INTRAVENOUSLY.*

Dose of Congo red, mg. per kg.	No. of rabbits.	Control.	5 min.	1 hr.	3 hrs.	24 hrs.	36 hrs.	Daily dye for 7 days.	Daily dye for 14 days.
10	5	212 (C) 57 (B)	173 (C) 42 (B)	207 (C) 46 (B)	240 (C) 61 (B)				
25	9	290 (C) 119 (B)	210 (C) 141 (B)	267 (C) 88 (B)	420 (C) 80 (B)	285 (C) 130 (B)	... ...	315 (C) 132 (B)	345 (C) 110 (B)
50	5	297 (C) 97 (B)	285 (C) 150 (B)	301 (C) 155 (B)	... ...	215 (C) 112 (B)	285 (C) 135 (B)	405 (C) 135 (B)	365 (C) 80 (B)
100	2	230 (C) 132 (B)	... ...	1200 (C) 850 (B)	... ...	242 (C) 227 (B)	265 (C) 157 (B)		

* (C) means coagulation time; (B), bleeding time, each in seconds.

Therefore, these negative results in rabbits, which received extra-therapeutic doses of Congo red, at least for certain disease states, refute the positive claims made for shortening of blood coagulation and bleeding times. Any small tendencies in this direction were well within the range of normal variations and of experimental error. The greatest decreases occurred 5 minutes and 1 hour after 10 and 25 mg. per kg. of the dye and here the maximum shortening amounted to an average of only 25%. With doses of more than 50 mg. per kg., bleeding and coagulation times were prolonged in

all animals. For instance, 100 mg. per kg. increased the coagulation time about 500% at the end of 1 hour, with a return to normal in 24 hours. This effect of large doses of the diazo dyes is well known and has been carefully investigated by Huggett and Rowe.[2] Of course, the effects of Congo red in clinical pathologic states of the blood might be different from those in healthy rabbits, but the opportunity of investigating clinical conditions was not available to me. At the same time, positive claims have been made for the dye in normal individuals and it has been injected routinely in connection with surgical operations. The character of the evidence to date does not justify its routine use, but further study in pathologic states may be worthwhile.

Conclusions. 1. Congo red in concentrations of 1 to 1000 protects against hemolysis of human erythrocytes by hypotonic saline solution, hypertonic urea and sodium taurocholate in saline solutions and saponin in dextrose and saline solutions. No protective action, but in fact increased hemolysis, occurs with Congo red in hypotonic dextrose solution and in ether and urea in aqueous solutions.

2. The antihemolytic action of Congo red appears to be mediated through a film effect on the cells, as the result of a change in the physical state of the dye, since Night Blue and salt, which increase the flocculation or precipitation of Congo red, also increase its protective action for erythrocytes.

3. Intravenous doses of 10 to 50 mg. per kg. Congo red in rabbits produce no consistent or demonstrable effects on hemoglobin, red blood cells, platelets and reticulocytes. Doses of 100 mg. per kg. produce a slight temporary anemia, with hemagglutination.

4. Single intravenous injections of more than 25 mg. per kg. of Congo red in rabbits cause a moderate leukocytosis, chiefly increases in the number of neutrophils and marked increases in sedimentation rate of blood.

5. Small or large extratherapeutic doses of Congo red in healthy rabbits produce no demonstrable or consistent and sufficient shortening of the blood coagulation and bleeding times, contrary to positive, though uncontrolled, claims in the literature. On the contrary, very large doses of the order of 100 mg. per kg. produce uniform anticoagulating effects.

6. Accordingly, the alleged clinical hemostatic action of Congo red, at least in normal individuals, lacks the support of controlled experimental evidence, but the action might be different in pathologic states.

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BRONCHOGRAPHIC STUDY OF APPARENTLY HEALED LUNG ABSCESSES.*

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The disappearance of the roentgenographic shadows of a lung abscess and its surrounding pneumonitis and the loss of symptoms referable to the abscess are usually accepted as conclusive evidence that the abscess has healed. Reports of the recurrence of lung abscesses,[1,2,4,5,11] suggest that these criteria of healing are insufficient.

Since the history, the physical examination and ordinary roentgenograms in these cases yield data that are consistent with the idea that healing of the abscess is complete, further investigation of the relationship of the residual condition of the lungs involves the use of bronchography.

Bronchography has been used for many years[7] in selected cases of pulmonary tuberculosis to determine the effectiveness of thoracoplasties in closing cavities and to demonstrate the presence of bronchiectasis as the source of persistent sputum in the absence of demonstrable pulmonary cavity. It has been used more extensively in the study of bronchiectasis and the acute, subacute and chronic phases of lung abscesses. A review of the literature, however, failed to reveal any account of the routine bronchographic study of apparently healed abscesses. Overholt,[8] to be sure, used bronchograms to determine the immediate results of operations upon lung abscesses. Farinas[6] followed with bronchograms the course of lung abscesses through their acute, subacute and chronic phases.

Amberson[1] and his associates have not reported their extensive experience with bronchography in the follow-up of apparently healed lung abscesses during the past 7 or 8 years. They have quite regularly found residual cavities or bronchiectasis. It has been their experience that these cases are more likely to have a recurrence, much more likely to bleed in later years, and are more subject to slow convalescence from ordinary respiratory infections. In cases treated by various measures, shown to be healed (including bronchograms), and allowed sufficient convalescence, they seldom observed recurrence. Amberson recommends a 6 months' period of convalescence in cases of acute lung abscesses.

In the following group of case histories are reported the results of bronchographic study of 6 patients whose abscesses were regarded as healed, as judged by the usual criteria. The contrast medium used in all cases was lipiodol. Both the supraglottic drop method and the intra-tracheal catheter method were used. All injections were made under fluoroscopic control.

* Read at regular meeting of Grasslands Hospital Staff, September 28, 1938.

Case Abstracts. CASE 1.—D. H., a negro female, aged 36, was admitted to the hospital with a diagnosis of intestinal obstruction. Four days following a laparotomy, at which time the intestinal obstruction was reduced, she began to cough and expectorate blood-tinged sputum. A roentgenogram revealed pneumonitis in the right upper lobe. Within a week an abscess cavity appeared in this area (Fig. 1) and the patient was expectorating large amounts of foul sputum. She was treated by postural drainage and weekly bronchoscopies. Three months after admission the patient was asymptomatic and an ordinary roentgenogram revealed no abnormality other than light fibrosis at the site of the abscess (Fig. 2). A bronchogram 1 month later (Fig. 3) revealed a defect interpreted as a remnant of the abscess cavity, though the patient remained asymptomatic.

CASE 2.—T. P., a white female, aged 43, was referred to the hospital for cholecystectomy. An adenoma of the thyroid with toxic symptoms was discovered and a thyroidectomy was done. The cholecystectomy was deferred. The postoperative course was uneventful after the first few stormy days, and the patient was discharged. A few days later she was readmitted with fever, cough and purulent sputum. A roentgenogram revealed an abscess in the upper portion of the right lung. After 3 months on a regimen of postural drainage and weekly bronchoscopies, the patient was asymptomatic and the roentgenogram revealed only light fibrosis at the abscess site. Six months later the patient was still asymptomatic, but a bronchogram revealed bronchiectasis in the upper part of the right lung.

CASE 3.—M. G., a white female, aged 37, developed an abscess in the upper portion of the left lung, immediately following a tonsillectomy. The temperature rose to 104° F. daily and the sputum became copious and foul 1 week later. The results of postural drainage and bronchoscopies were unsatisfactory and the abscess was drained surgically 3 months after its onset. It was opened more widely 6 weeks later, in order to improve drainage. The patient was discharged as cured of her abscess, but with a residual broncho-pleuro-cutaneous fistula, 6 months after the onset of the abscess. The fistula closed 1 month later. A bronchogram revealed bronchiectasis and a cavity remnant at the site of the abscess, 21 months after discharge, though there had been no recurrence of symptoms.

CASE 4.—M. H., a white female, aged 30, gave a history of having had a lung abscess in the upper portion of the right lung 21 years previously. The abscess had been drained surgically with an uneventful recovery. Subsequently, the patient had frequent colds, during which she would expectorate purulent sputum. A small hemoptysis occurred soon after she came under our observation. Examinations of the sputum for tubercle bacilli were negative and roentgenograms revealed no abnormality except light fibrosis and postoperative deformities of the ribs in the right hemithorax (Fig. 4). A bronchogram (Fig. 5) revealed bronchiectasis and a defect interpreted as an abscess remnant in the upper portion of the right lung. At this time the patient was expectorating 60 cc. of foul pus daily.

CASE 5.—A.M., a white male, aged 33, was admitted to the hospital complaining of cough and the expectoration of 3 ounces of foul pus daily. His pulmonary symptoms had begun with an episode of more acute illness 18 months previously, but he had had no treatment. On admission, slight cyanosis was present and the fingers were clubbed. He was afebrile. A roentgenogram (Fig. 6) revealed pneumonitis surrounding a rarefaction in the upper part of the right lung. The patient remained on a sanatorium regimen of modified bed rest with postural drainage and weekly bronchoscopies for 5½ months. The sputum was repeatedly negative for tubercle bacilli and decreased to ½ ounce. Upon discharge the pneumonitis had cleared, but the rarefaction persisted (Fig. 7). A bronchogram 2½ years

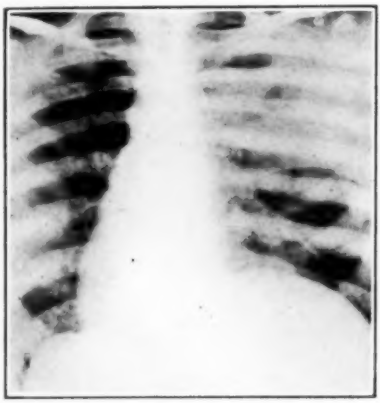

FIG. 1.—D.H.; acute lung abscess, upper part right lung.

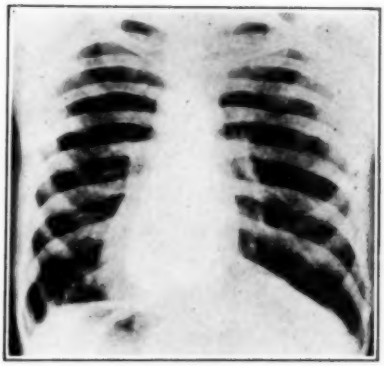

FIG. 2.—D.H.; 3 months later: lung abscess apparently healed.

FIG. 3.—D.H.; 1 month later: bronchogram.

FIG. 4.—M.H.: 21 years after surgical drainage of lung abscess, mid-portion right lung.

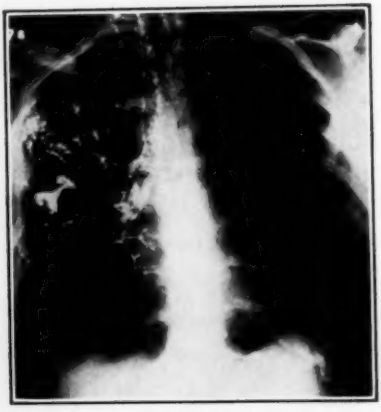

FIG. 5.—M.H.; bronchogram.

FIG. 6.—A.M.: recurrent pneumonitis upper part right lung.

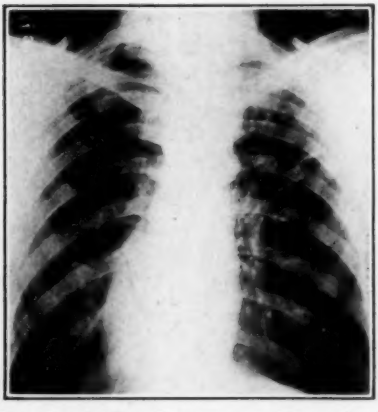

FIG. 7.—A.M.; after pneumonitis resolved, 5 months later.

FIG. 8.—A.M.; bronchogram, 2½ years later.

later (Fig. 8) revealed a large cavity remnant, as well as bronchiectasis, though the patient had remained asymptomatic.

Case 6.—C. H., a white female, aged 44, was admitted to the hospital with the following history: 8 months previously she had a tonsillectomy under ether anesthesia. Two weeks later she developed a right upper lobe abscess with fever, cough and large amounts of foul sputum. Five weeks later the cough and expectoration ceased. Two months later the symptoms recurred, and continued until admission to Grasslands. Three weeks before admission, a 2-ounce hemoptysis occurred. Acid-fast bacilli were found in the sputum on 5 occasions before admission. Postural drainage and bronchoscopy were used for a few weeks after admission, but the abscess progressed and surgical drainage was done, with excellent clinical results. Acid-fast bacilli were found in the pus obtained from the abscess at operation, but these failed to produce tuberculosis in guinea-pigs. Ten months after admission the patient was discharged. Though she was asymptomatic, and the ordinary roentgenograms revealed only light fibrosis and postoperative rib deformities over the abscess site, a bronchogram revealed bronchiectatic sacs in the involved area. During a subsequent period of 2½ years, the patient has remained asymptomatic.

Discussion. The bronchopulmonary defects that can be demonstrated after healing of an abscess apparently has occurred, are of two kinds: cavitary and bronchiectatic. The cavitary defect probably represents an arrested stage of the fibrotic contraction of the abscess cavity. As such, it should be regarded as something less than the theoretically attainable end-result of healing. The cavitary remnant is not as commonly present as is the bronchiectasis. Pinner's concept[9] of the unity of bronchopulmonary suppuration explains the frequent incidence of bronchiectatic remnants. He demonstrated that all phases of bronchopulmonary suppuration (pneumonitis, purulent bronchitis, bronchiectasis, abscess and gangrene) are characteristically present in some degree in most bronchopulmonary suppurative lesions. From the viewpoint of the pathologist, therefore, it is incorrect to designate one lesion as a lung abscess, another as bronchiectasis, and another as gangrene of the lung. It is the particular type of lesion which happens to predominate which determines the clinical diagnosis. Farinas[6] showed that bronchiectasis commonly involves the bronchus draining an abscess and that bronchiectasis often develops in other parts of the lungs in cases of persistent abscesses.

The permanence of bronchiectasis is generally recognized. It may progress, or remain stationary, but regression of the bronchial defects is not to be expected. Rist's experience with the treatment of bronchiectasis by pneumothorax[10] emphasized the characteristic persistence of bronchiectatic defects after symptoms referable to them have ceased. It is well known that these symptoms wax and wane as the infectious processes in and around the bronchi recur and subside. Churchill[3] has emphasized the fact that bronchiectasis is a persistent and often progressive disease and that extirpation of the diseased portion of the lung offers the only real cure.

Reports of the cure of bronchiectasis are probably based upon the recession of symptoms rather than disappearance of the bronchiectasis. It seems logical, therefore, to look upon bronchiectatic residues after lung abscesses as being potentially dangerous and Amberson's experience has proven this.

Conclusions. 1. Bronchographic study after the disappearance of the symptoms and the roentgenographic shadows of acute suppurative bronchopulmonary disease often reveals residual pathologic defects in the lung and bronchi that are otherwise unrecognizable.

2. Bronchographic study should be used routinely to determine the residual state of the bronchi and lung after the symptoms and the roentgenographic shadows of the acute suppurative process have disappeared.

3. The clinical concept of healing of acute suppurative bronchopulmonary processes should be broadened to include the residual pathologic changes in the lungs and bronchi.

The author is indebted to the staff of the Medical and Surgical Services of Grasslands Hospital for the opportunity to study the presented cases.

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A CLINICAL STUDY OF ALUM-PRECIPITATED INSULIN.

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The introduction of protamine-insulin marks an advance in the therapy of diabetes. Because of its slow rate of absorption, a single subcutaneous injection of protamine-insulin serves as a depot sufficient to supply the patient's needs for 24 hours or longer. However, there are certain features which occasionally detract from the value of this preparation. Its hypoglycemic activity does not begin until

about 6 hours after injection. In order to tide the patient over this initial period an additional injection of ordinary insulin is sometimes required. Furthermore, the duration of the hypoglycemic action of protamine-insulin is not always uniform so that insulin shock may occur as late as 24 hours after injection. Finally, some authors[2] have expressed the opinion that the parenteral administration over a number of years of small amounts of a foreign protein, such as protamine, may induce undesired reactions. Hence, it seemed of interest to investigate the therapeutic efficiency of other compounds of insulin precipitated with non-protein substances. For this purpose the alum-precipitated insulin, described in our earlier report,[1] was chosen.

Alum-precipitated insulin is prepared by adding 10 cc. of a 50% solution of $NaAl(SO_4)_2 12H_2O$ to 100 cc. of Insulin U 40. After remaining in the refrigerator for 24 hours the copious precipitate which forms is centrifuged off from the supernatant fluid. To the latter, another portion of 10 cc. of 50% soda-alum solution is added. After 24 hours of refrigeration a second precipitate is obtained by centrifuging. The combined precipitates are suspended in 50 cc. of saline of pH 6, preserved with 0.2% phenol and distributed into ampules for administration to patients. In preliminary experiments, it was found that by dissolving the combined precipitates in solutions of pH 1 to 2 and assaying the resultant clear solution on rabbits, a quantitative recovery of the original insulin unitage was obtained. Thus, one unit of alum-precipitated insulin refers to one unit of ordinary insulin precipitated by alum.

For the present investigation we selected 12 diabetic patients, most of whom required large amounts of insulin (up to 160 units) daily in 3 or 4 divided doses. Two of these patients were juvenile diabetics. All of them had been watched over a period of years in the dispensary of the Israel Zion Hospital where adjustments of their caloric and insulin requirements had been made from time to time.

Case Abstracts. Case 1.—N. P., white female, aged 43, diabetic for 12 years, has been taking insulin since 1924. Average amount 150 units daily (8 A.M.—40 units, noon—30 units, 6 P.M.—40 units, 9 P.M.—40 units). In spite of this treatment has had from 2 to 9% of glucose in the urine, with a total daily output of 2 to 4 liters. Has frequently manifested shock symptoms, especially diplopia, when blood glucose fell below 170 mg. per 100 cc.; had been hospitalized 4 times in the past 3 years, twice in coma and twice in insulin shock. Weight 162 lbs. (74 kg.).

The first administration of the alum-precipitated insulin was given on November 6, 1936, when 160 units were injected at 10 A.M. in 1 dose. Meals were served to the patient according to her usual routine: breakfast, 100 calories at 9 A.M.; lunch, 900 calories at 2 P.M.; and dinner, 600 calories at 8 P.M. No untoward effects were observed. Neither local nor systemic reactions occurred. Hourly determinations of the blood glucose were made and the results were given in the chart. The patient was continued on this treatment for 2 months, during which time she showed a maximum of 1% and a minimum of a trace of glucose in the urine. The fasting blood glucose

ranged from 170 to 190 mg. in 100 cc. After this period she began complaining of slight dizziness, sweating and hunger at about 2 P.M. (5 hours after the injection of the alum-precipitated insulin).

The blood glucose at this time was 160 mg. per 100 cc. The daily dose of insulin was therefore reduced to 130 units in a single early morning injection. For a further period of 3 months the patient was maintained on the same amount of insulin. She felt quite well. Blood fasting sugar was 180 to 190 mg. per 100 cc. At the end of this period, because of reappearance of hypoglycemic symptoms, the insulin dosage was still reduced down to 100 units. In December, 1937, she developed an upper respiratory infection in the course of which the glucose tolerance was lowered and she had from 2 to 4% urinary glucose. The daily alum-precipitated insulin dosage was therefore raised to 130 units for the duration of the infection (9 days). This amount was reduced again to 100 units after the patient's condition improved.

At present, after about 2 years, she is still being comfortably maintained on 100 units of the alum-precipitated insulin. Present weight (September, 1938) 168 lbs. (77 kg.).

CASE 2.—L. B., a white female, aged 58, diabetic for 25 years, has been taking 50 to 75 units of old insulin daily since 1924 in 2 or 3 divided doses. Her urine has never been entirely sugar-free, excreting daily (between 1932 and 1936) from traces to 75 gm. of glucose. The treatment with alum-precipitated insulin was started November 11, 1936. Fifty units of alum-precipitated insulin were injected just before breakfast. Her regular morning, noon and evening meals were given at the usual time. No local or systemic reactions were noted. The blood glucose curve, after the injection, is given in the chart.

This amount of insulin was continued for a period slightly over 2 months. On January 14, 1937, she began complaining of tingling and numbness in the fingers and slight sweating and hunger. A blood specimen taken during one of these episodes showed 140 mg. %. The alum-precipitated insulin was therefore reduced to 35 units, on which dosage she is being maintained with a fasting blood sugar ranging between 130 to 180 mg. % and urinary glucose between 0 and 0.5 %. She is comfortable and has gained weight.

CASE 3.—Mrs. A. H., Jewish female, aged 48, diabetic for 10 years, obese and difficult to control; sensitive to all known varieties of insulin, manifesting a severe generalized urticaria after injections. She was slowly desensitized by injections of very minute doses of old insulin, beginning with 0.001 unit and slowly increasing the dose until she tolerated 60 units of old insulin daily. During the first 10 months in 1936, she was given 40 to 50 units of old insulin in 3 doses. During that period, her average fasting blood glucose was 258.6 mg. per 100 cc. and the daily urinary glucose output was 18 to 75 gm. On November 11, she was injected with 50 units of alum-precipitated insulin before breakfast. Her routine breakfast, dinner and supper were given and hourly blood glucose determinations were made. These appear in the chart.

After 3 months of treatment with alum-precipitated insulin, she began showing mild hypoglycemic symptoms (sweating, hunger, etc.). Therefore, her alum-precipitated insulin was reduced to 40 units daily. At no time did she show local or systemic ill effects. The patient is still being well maintained on this amount of insulin. Her last fasting blood glucose in September, 1938, showed 210 mg. % with a urine glucose of 0.5%.

CASE 4.—Mrs. C. F., white female, aged 63, a known diabetic since 1932, has been taking 20 to 45 units of old insulin daily in 2 doses; has had from traces to 3.3% of urinary glucose, with average fasting blood sugar (from 1932 to 1936) of 223 mg. per 100 cc. In 1936 (Sept. 12) she was injected with

30 units of alum-precipitated insulin, using the same routine as in the previous case.

Blood glucose fluctuation was determined as shown in the chart. On Sept. 25, 1936, she gradually developed hypoglycemic symptoms, drowsiness, hunger and sweating at about 4 P.M. At this time, she was aglycosuric with a blood sugar of 100 to 120 mg.%. Insulin dose was reduced to 24 units, on which amount she is still being maintained. Her present weight is 129 lbs. (as against 126 lbs. in 1936). She feels well.

CASE 5.—R. G., white female, aged 52, a known diabetic since 1927, has been using 45 to 55 units of old insulin in 3 doses daily, excreting 40 gm. of glucose daily. Fasting blood sugar, in the period of 1930 to 1936, ranged from 159 mg. to 233 mg. per 100 cc. On May 20, 1937, she was injected with 45 units of alum-precipitated insulin before breakfast. The blood glucose variations are shown in the chart. Has continued on this regimen since that time. She is comfortable and has gained 3 lbs. Last fasting blood glucose, Sept. 10, 1938, 130 mg. per 100 cc.

TABLE 1.—BLOOD GLUCOSE FINDINGS AFTER INJECTIONS OF ALUM-PRECIPITATED INSULIN.

Pt.	*Case No.*	*1 hr.*	*2 hrs.*	*3 hrs.*	*4 hrs.*	*5 hrs.*	*6 hrs.*	*7 hrs.*	*8 hrs.*	*9 hrs.*	*10 hrs.*	*11 hrs.*	*12 hrs.*	*23 hrs.*	*24 hrs.*
N. P.	1	262	278	286	288	270	211	190	142	148	138	140	142	242	258
L. B.	2	224	230	216	210	194	178	142	128	118	94	82	80	230	242
A. H.	3	264	278	242	222	190	184	172	152	132	124	118	138	228	250
G. F.	4	234	210	186	174	152	140	122	111	96	88	104	96	220	236
R. G.	5	182	170	158	166	148	132	118	98	90	96	94	108	194	188
D. G.	6	188	196	210	178	152	134	110	104	108	89	108	110	166	172
L. G.	7	234	231	210	172	134	120	108	104	102	101	96	107	188	194
R. C.	8	262	241	228	234	218	184	162	128	108	118	124	142	284	290
S. C.	9	310	298	248	228	196	178	166	170	164	154	196	190	286	278
J. R.	10	181	170	168	140	138	136	121	119	121	118	126	138	178	188
S. R.	11	168	144	156	139	138	121	101	99	108	118	138	146	160	166
A. A.	12	158	164	139	121	118	111	101	89	111	118	120	121	144	151

CASE 6.—Mrs. G., Jewish female, aged 62, known diabetic for 15 years, fairly well controlled during that period with 45 to 60 units of old insulin daily in 3 doses. Average fasting blood glucose 175 mg. per 100 cc., urine sugar ranging from traces to 1%. Sixty units of alum-precipitated insulin injected on Dec. 16, 1936. No untoward effects observed. Blood glucose curve is given in the chart. At present, 15 months later, she is still well maintained on single morning doses of 50 units of alum-precipitated insulin. She is comfortable and has gained 5 pounds in the last year.

CASE 7.—L. G., Jewish male, aged 22, a juvenile diabetic of 10 years' duration, weight 110 lbs., height 65 inches. Has been taking 120 units of old insulin daily in 4 doses of 30 units each at 9 A.M., noon, 4 P.M., and 8 P.M. Frequent episodes of coma and hypoglycemic tetany have occurred, necessitating hospitalization on several occasions. Average glycosuria 1 to 8%, with total daily urine output of 2 to 3 liters. Fasting blood glucose ranged from 180 to 330 mg. per 100 cc. On March 10, 1936, 120 units of alum-precipitated insulin were injected. The blood glucose variations are given in the appended chart.

Up to Sept. 17, 1937, the patient was well controlled. At 6 P.M. of that day, an insidious onset of hypoglycemia manifesting itself by drowsiness deepening into stupor. After taking 2 glasses of orange juice, containing 40 gm. of glucose, the patient quickly rallied. No further ill effects were

noticed and the daily dosage of alum-precipitated insulin was thereafter cut to 100 units. Since then, has been kept on the same high caloric, high carbohydrate diet with 100 units of alum-precipitated insulin daily administered in one early morning injection. Is feeling well and has been doing daily work, without interruption.

CASE 8.—R. C., Jewish white female, aged 12, an extremely severe juvenile diabetic of 7 years' duration, has been taking a total of 200 units of old insulin daily in 4 or 5 doses. Has manifested marked xanthochromia of several years' duration. In 1935 and 1936 was hospitalized 4 times because of diabetic coma. Diet consists of 1800 calories daily. Twenty-four-hour urine had from 2 to 5% glucose and, at times, as much as 9%. Average fasting blood glucose 250 mg. per 100 cc. On Dec. 14, 1936, 160 units of alum-precipitated insulin were injected. Blood glucose variations of that day appear in the chart.

After 10 months the child is still maintained well on the same diet and the same amount of alum-precipitated insulin, with an average 24-hour urine sugar of 0.5 to 1% and an average fasting blood sugar of 180 mg. per 100 cc. On two occasions infections at the site of the injections were observed. This was traced to faulty technique in the administration of the insulin by the patient's mother. The child has gained weight, felt well and was able to attend school uninterruptedly for the past 2 years, which was impossible under previous treatment with old insulin.

CASE 9.—S. C., white female, aged 55, a known diabetic of 5 years' duration. Condition was complicated by peripheral vascular and coronary diseases. Treatment consisted of 100 units of old insulin daily, in 3 doses. Has been hospitalized twice in the past 2 years for attacks of coronary thrombosis. Diet consisted of 1500 calories. Average 24-hour urine sugar in the past 3 years showed from traces to 1%. Average blood sugar 180 mg. per 100 cc. On Dec. 10, 1936, 120 units of alum-precipitated insulin were given in a single morning injection. Subsequent blood glucose of that day appears in the chart. No untoward effects were observed. Since then, has been maintained well on the same diet and the same amount of alum-precipitated insulin. Several repeated urine glucose tests in the past 16 months show from traces to 0.5%, with a fasting blood glucose of 160 mg.

CASE 10.—J. R., white male, aged 58, a known diabetic of 4 years' duration with fasting urine glucose fluctuating from 1.5 to 3%. Blood glucose May, 1937, was 189 mg. per 100 cc. Has been using 15 to 30 units of old insulin. On June 23, 1937, 20 units of alum-precipitated insulin were injected in 1 dose before breakfast. Blood glucose fluctuations of that day are given in the chart. Patient has been well maintained on a diet of 1500 calories, including 185 to 190 gm. of availiable glucose and 20 units of alum-precipitated insulin. Is comfortable and does his daily work without difficulty.

CASE 11.—S. R., Jewish male, aged 52, a known diabetic for 15 years, excretes an average of from 10 to 15 gm. of glucose daily, with a fasting blood glucose of 185 mg. Average ordinary insulin requirement had been 25 units daily in 2 doses. On March 17, 1937, 25 units of alum-precipitated insulin were injected, following the same technique as outlined above. Blood glucose curve of that day is given in the chart. Patient was maintained on his previous diet with 25 units of alum-precipitated insulin daily in a single injection. Is doing well, is able to do his usual work and has kept his weight stationary during the past 18 months (151 lbs.).

CASE 12.—A. A., Jewish female, aged 49, a known diabetic of 4 years' duration, has been excreting an average of 10 to 20 gm. of glucose daily in the urine, with an average fasting blood glucose of 160 mg. per 100 cc. Average old insulin requirement was 20 units daily in 2 divided doses. On March 21, 1937, 20 units of alum-precipitated insulin were injected. The resulting blood curve is given in the chart. Since that time, has been receiv-

ing the same amount of alum-precipitated insulin daily in one single injection. Condition remained good. Urine rarely showed glucose, and fasting blood sugars averaged 130 mg. per 100 cc.

Discussion. While the number of cases here reported is limited, yet the long periods of treatment during which several thousand injections were given and the uniform results obtained yield sufficient information to demonstrate the value of alum-precipitated insulin. The following facts stand out:

1. Alum-precipitated insulin is a safe preparation. It was administered in each case in a single morning injection equivalent to the total daily unitage of the old insulin which had previously been given in several injections. As much as 160 units of alum-precipitated insulin were used in a single dose (Case 1) without untoward effects, local or general.

2. The lowering of the blood glucose with corresponding drop of the urine glucose begins within 2 hours after injection of the alum-precipitated insulin. Thus, in not one of our cases was the use of a supplementary dose of ordinary insulin necessary. The hypoglycemic action reaches its maximum effect in 8 hours, after which it gradually wears off.

3. The effect of alum-precipitated insulin is more evenly distributed through the 24 hours. There were not noted marked fluctuations of the blood sugar or any delayed action beyond the 24-hour period. In this respect, it differs from protamine-zinc insulin, the injection of which not infrequently causes a delayed hypoglycemic action with symptoms of shock.

4. On only one occasion manifestations of hypoglycemic tetany were encountered, in a patient (Case 7) who had several hypoglycemic shocks during the 10 years of old insulin therapy. The shock was of short duration and the patient rallied quickly. Subsequently, the patient was able to tolerate the same dose of alum-precipitated insulin without ill effect.

5. In the course of treatment we were obliged to reduce the amount of alum-precipitated insulin which originally had been just sufficient to keep the diabetic status under control.

6. The physical and mental condition of the patients was good throughout the whole period of treatment. Some gained weight while others, who did not show any appreciable gain in weight, felt a general euphoria and were comfortable enough to perform their daily work.

Summary. 1. Alum-precipitated insulin like protamine-zinc insulin can be administered in one single dose covering the daily requirement.

2. The action of alum-precipitated insulin begins within 2 hours which obviates the necessity of administering a supplementary injection of old insulin.

3. The effect of alum-precipitated insulin wears off within 24 hours so that the fear of a delayed reaction is eliminated.

4. In the course of treatment with alum-precipitated insulin, the tolerance of the patients seems to improve and the amount of insulin may be reduced.

5. Alum-precipitated insulin contains no foreign protein which might have an undesirable effect in the course of prolonged administration.

6. Alum-precipitated insulin is stable, non-toxic even after prolonged administration and does not cause infiltrates at the site of injection.

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CIRCULATORY EFFECTS OF VOLATILE AMPHETAMINE (BENZEDRINE INHALER).

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In recent years a volatile compound, beta-phenyl-iso-propylamine (amphetamine), in the form of "benzedrine inhaler", has come into widespread use for the relief of congestion of the nasal mucous membranes. In view of the fact that this drug is closely related chemically and in some of its pharmacologic properties to the sympathomimetic drugs, ephedrine and epinephrine, it was considered advisable to inquire into its effects on the circulation, particularly in individuals with heart disease. The dangers attendant upon the administration of epinephrine and ephedrine in the presence of angina pectoris are now coming to be fully recognized and it appeared possible that under the same circumstances the "benzedrine inhaler" might produce undesirable reactions.

The scope of this study was limited to an investigation of the benzedrine inhaler. The circulatory effects of "benzedrine sulphate" have already been investigated elsewhere. Myerson *et al.*[1] observed the effects of benzedrine sulphate administered subcutaneously to 18 patients in doses of 9 to 50 mg. A gradual rise in the systolic blood pressure varying from 10 to 64 mm. Hg was noted in all but 1 case. The maximum rise was reached in 11 to 85 minutes and the pressure had returned to the original level in 1½ to 7½ hours. There was no commensurate rise in the diastolic

pressure. The pulse rate decreased coincident with the rise in systolic pressure in 12 cases, remained unchanged in 4 cases and increased in 2 cases. The decrease in pulse rate varied from 4 to 25 beats per minute.

There is no qualitative difference between the pharmacologic effects of benzedrine inhaler and benzedrine sulphate once absorbed into the circulation, but the amount of the drug actually absorbed from the inhaler is very small. Each tube of the inhaler contains 325 mg. of benzedrine. It has been estimated that at each average inhalation from a fresh tube 0.05 mg. is taken out of the tube. Some of this is lost in exhalation and probably only a relatively small fraction enters the circulation.[2] According to the directions on the tube, not more than 2 inhalations from each nostril should be taken within the course of 1 hour, making a maximum recommended dose of 0.2 mg. per hour. The effects of fantastically large amounts of the benzedrine inhaler in a normal individual were investigated by Waud,[3] who in repeated experiments with a tube of benzedrine inhaler in each nostril inhaled entirely through the tubes for periods of 4 to 6 hours. He estimated that the dose taken was 1000 times the recommended therapeutic dose. He noted a rise in the pulse rate and in both systolic and diastolic blood pressures. He also developed extrasystoles which persisted for 4 or 5 days after an experiment and on 2 occasions had paroxysmal tachycardia following cessation of the inhalations.

Procedure. A total of 67 individuals was studied. Ten of these were controls without heart disease, 10 cases of rheumatic heart disease, 1 syphilitic, 10 hypertensive, and 36 cases of arteriosclerotic heart disease, 8 of them with congestive failure without angina and 28 with angina pectoris.

In each case, a control record was made of the pulse, blood pressure and electrocardiogram. Then the patient took 5 deep inhalations of benzedrine inhaler in each nostril in the course of 2 minutes. Fresh inhalers were used in each case. Electrocardiograms were recorded during and immediately after the inhalations, 5 minutes, and one-half hour later. Blood pressure readings were noted before and 5 minutes after the inhalations.

RESULTS. *Controls.* One intern and 9 patients convalescing from various non-circulatory diseases were used as controls. Six of them were males and 4 females and they were from 23 to 40 years of age. Changes in the pulse rate and blood pressure levels were so slight and so variable as to be regarded as entirely without significance. There was no change in the electrocardiogram.

Rheumatic Heart Disease. There were 10 patients with rheumatic heart disease; 2 of these had active rheumatic fever and 2 others had auricular fibrillation. Three were females and 7 males, the ages varying from 13 to 58 years. Following the inhalation of benzedrine there was no significant alteration in pulse rate or blood pressure. Electrocardiograms showed slight changes in 2 instances. In 1 case the *T* wave in Lead III which was inverted in the control

record changed to an upright deflection in subsequent records. In another case, there was a slight but definite shift in the axis to the left at the end of one-half hour. These changes were not regarded as definitely significant.

Syphilitic Heart Disease. In 1 case of a man of 46 with syphilitic aortic regurgitation and congestive failure, no significant changes in pulse, blood pressure or electrocardiogram were observed following the use of benzedrine inhaler.

Hypertensive Heart Disease. This group included 10 cases, 6 female and 4 male aged from 15 to 70 years. In each case, the systolic blood pressure was above 210 mg. Hg or the diastolic pressure was above 105 mg. Hg. The youngest patient had chronic glomerular nephritis. Four of the cases were in congestive failure at the time the tests were made. In this group, likewise, benzedrine inhaler had no effect on pulse, blood pressure or electrocardiogram.

Arteriosclerotic Heart Disease. This group consisted of 36 cases, 28 of whom were suffering from typical angina pectoris. Of the 8 cases without angina, 2 had had a previous coronary thrombosis and all had had symptoms or signs of cardiac failure. None of these 8 showed significant changes in pulse, blood pressure or electrocardiogram following the inhalation.

Angina Pectoris. Fifteen of the cases with angina pectoris were female and 13 were male, the ages varying from 37 to 76 years. Eight of them had had a previous history of coronary thrombosis. No significant alterations in pulse rate, blood pressure or electrocardiogram were noted in this group. In 1 patient, however, the inhalation of benzedrine was followed by an attack of angina pectoris. The following is a summary of the observations in this case.

Case 1.—A 48-year-old housewife had had a typical attack of coronary thrombosis 14 months before, following which she had attacks of pain in the left chest radiating down the left arm. These attacks were associated with a choking sensation. They were precipitated by exertion or eating and lasted only a few minutes. During the first test she complained of slight precordial distress after 5 or 6 inhalations of the benzedrine (over a period of less than 2 minutes). On the next day, the same procedure was carried out using a tube which to all outward appearance was the same as the one used the day before, but which contained only the menthol and lavender with which the benzedrine is regularly compounded. No reaction was noted with this control. About 10 minutes later she was given a tube containing the regular formula to inhale and after 6 or 7 inhalations experienced an attack of moderately severe precordial pain which was relieved after the administration of $\frac{1}{100}$ gr. of nitroglycerine. No changes in the electrocardiogram were observed in association with these attacks.

About 3 weeks later another test was carried out. On this occasion, she developed a typical attack of angina following 3 inhalations of the benzedrine. The pain was relieved by nitroglycerine, gr. $\frac{1}{50}$. The electrocardiogram showed no change. The significant feature of this test was that angina appeared to be precipitated by an amount of benzedrine in the range of the therapeutic dose recommended by the manufacturer. About 10 minutes later the patient was given 6 inhalations of a "blank" tube containing only menthol and lavender without provoking any symptoms.

Discussion. It seems justifiable to interpret the painful attacks which in this case appeared to be related to the inhalation of benzedrine as angina pectoris. In 3 other cases precordial symptoms attended the initial use of the inhaler, but subsequent control tests using both the regular and "blank" tubes failed to substantiate any relationship between the drug and the symptoms. It is of some interest that the patient who was most incapacitated by his angina had no symptoms from inhalation of benzedrine, nor did the patient with the most abnormal electrocardiogram.

Summary and Conclusion. The effects on the circulation of volatile amphetamine (benzedrine inhaler), in larger than therapeutic doses, were studied in 10 individuals with normal hearts and 57 patients with various forms of heart disease.

No significant effect on the pulse or blood pressure and only occasional, slight and probably insignificant effects on the electrocardiogram were observed.

In 1 of 28 cases of angina pectoris, attacks of angina appeared to be precipitated by the drug.

The above observations lead to the conclusion that heart disease *per se* is not a contraindication to the use of benzedrine inhaler in therapeutic doses. Nor does there appear to be any pressor effect to contraindicate its use in hypertension. On the other hand, in patients who have had angina pectoris it should be used with caution, if at all, since in occasional cases it may precipitate an attack.

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BOOK REVIEWS AND NOTICES

PRACTICAL MICROBIOLOGY AND PUBLIC HEALTH. For Students of Medicine, Public Health and General Bacteriology. By WILLIAM BARNARD SHARP, S.M., M.D., PH.D., Professor of Bacteriology and Preventive Medicine in the Medical Department of the University of Texas; Visiting Bacteriologist of John Sealy Hospital, Galveston; etc. Pp. 492; 125 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, $4.50.

THIS book is intended to accompany courses in "Preventive Medicine" or "Public Health," being given to medical students. The author presents the volume only as a handbook "designed to aid the student in organization, interpretation, and systematic record of data from laboratory and field." It is in no sense a textbook, nor does it do more than present the barest essentials, in synoptic form, of such a variety of subjects as general and clinical bacteriology and mycology; vehicles of infection; immunology; the methods used by the public health laboratory in examining milk, water, and foods, and in making various diagnostic tests; public health field surveys; garbage removal; ventilation; housing; restaurants; vital statistics; epidemiology; protozoölogy; helminthology; etc. It is expected of the student that he be previously "Familiarized by lecture and standard tests with the findings of authorities. . . ." The book is attractively printed and bound, and instructively illustrated. A number of laboratory exercises are detailed or suggested, and an index is appended. K. M.

SYNOPSIS OF CLINICAL LABORATORY METHODS. By W. E. BRAY, B.A., M.D., Professor of Clinical Pathology, University of Virginia; Director of Clinical Laboratory, University of Virginia Hospital. Pp. 408; 51 illustrations and 17 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1938. Price, $4.50.

THE text covers the entire range of practical procedures in Clinical Pathology, including most of the more recently developed methods. Alternate techniques for the same purpose are well selected and not too numerous. The text is brief, concise. Illustrations and tables are good. The book is commendable for its information in the selection and interpretation of methods, thus emphasizing the practical application of Clinical Pathology in diagnosis. W. B.

DIE ENDOKRINEN DRÜSEN DES GEHIRNS. Epyphyse und Hypophyse. Ein Blick in ein interessantes Gebiet. By DR. MED. PAUL NIEHANS, Chirug. F. M. H. der Klinik von Clarens und der Spitäler von Vevey und Montreux (Schweiz). Pp. 280. Bern: Medizinischer Verlag Hans Huber, 1938. Price, Fr. 10.50.

THE author has attempted an exceedingly difficult task, that results in an essentially uncritical compilation of conclusions from the abundant literature concerning the pituitary and pineal glands. The discussion of the etiologies of clinical syndromes is replete with statements based on very poor evidence. No bibliography is given. F. D.

DISEASES OF THE EAR, NOSE AND THROAT. By FRANCIS L. LEDERER, B.Sc., M.D., F.A.C.S., Professor and Head of the Department of Laryngology, Rhinology and Otology, University of Illinois College of Medicine; Chief of the Otolaryngological Service, Research and Educational Hospital. Pp. 835; 457 illustrations, and 16 color plates. Philadelphia: F. A. Davis Company, 1938. Price, $10.00.

THE author of this textbook has courageously adopted numerous innovations which tend to enhance the value of a reference volume. Although profusely illustrated, there is no attempt at illustration of surgical procedures which, with slight variations, are portrayed with monotonous regularity in most otolaryngological textbooks. The author achieves throughout a clear presentation of etiology, pathology, symptomatology, diagnosis, prophylaxis and treatment. While the appropriate surgical measures are described where indicated, they are relegated to minor emphasis. The author's clear exposition of the anatomy and physiology of the ear, the nose and paranasal sinuses, the pharynx and the larynx is especially instructive and satisfying. The text is arranged in two columns to facilitate reading; the illustrations are excellent. A determined attempt has been made to present the fullest details in diagnosis, differential diagnosis and therapy. The subject matter includes such considerations as diseases of the tongue, and of the salivary glands and ducts. The technique and instrumentation of bronchoscopy and esophagoscopy are described; separate chapters are devoted to otolaryngological symptoms common to many diseases, facial neuralgias, allergy, disorders of speech, psychiatric aspects and legal medicine. While no bibliographic references are given, the index is complete and detailed. This volume is an outstanding addition to the textbooks in the field of otolaryngology. H. S.

DENTAL SCIENCE AND DENTAL ART. Edited by SAMUEL M. GORDON, PH.D., National Research Council Fellow (Biological Sciences), 1926–1928; Director, American Dental Association Bureau of Chemistry and Secretary of the Council on Dental Therapeutics, American Dental Association, 1928–1937. Nineteen Contributors. Pp. 731; 224 illustrations and 61 tables. Philadelphia: Lea & Febiger, 1938. Price, $9.50.

THOSE who still believe that modern dentistry has not emerged from the mere mechanical stage should read this elaborate composium edited by Dr. Gordon. It is written in the form of separate essays on the physiologic, pathologic and therapeutic problems in dentistry which point definitely to a new era in dental science and dental art.

Dr. Gordon's selection of authors and especially his correlation of subject matter is commendable. Most essays mention possibilities of investigation, thus stimulating research in their respective fields.

Schour covers tooth development and the effect of avitaminosis and endocrine inadequacies on developing and adult teeth, their attachment apparatus, the form and function of the dental arches, the jaws and the cranium. In his discussion of dental fluorosis he fails to refer to the exhaustive essay of Chaneles on fluorine and experimental fluorosis, which anteceded his work by four years. Schour's attitude appears too definite in regard to the impossibility that calcium may be withdrawn from tooth structures. In 1938 Hevesy, Holst and Krogh showed that radio-activated phosphorus atoms are exchanged. The condensed results of various studies of Roentgen ray diffraction patterns throw an interesting light on the crystal structures of enamel and dentin. Gottlieb and Orban write on the biology of the investing structures of the teeth and outline some pathologic conditions of these tissues. Brodie presents the biologic aspect of orthodontia. Here we should like to have seen the subject of diet treated more extensively

and regret the omission of nutritional considerations. Babkin's essay on the physiology of the salivary gland seems both up to date and comprehensive. His list of references is creditable. The subject of salivary calculus is well presented by Karshan. Rosebury reviews the problem of dental caries extremely well; the biochemical aspects of dental caries are done by Karshan; the bacteriologic and immunologic features by Jay, who states at the end of his chapter: "It is still problematical whether the immunologic approach will yield practical results, and as stated at the beginning, the whole problem of immunity in dental caries is atypical but the pursuance of these studies may ultimately lead to findings of considerable significance." Gordon reviews the essential factors in calcium metabolism, absorbability of calcium salts, inorganic *vs.* organic calcium phosphorus combinations, nutritional and pharmacodynamic actions of calcium compounds, and guided by an array of modern writers on the subject discusses the aspects of calcium metabolism of direct interest to the dentist. The bacteriologic aspect and possible predisposing factors of Vincent's infection are well covered by Rosebury, whereas Lyons' essay on the clinical manifestations, pathologic phenomena and therapeutic measures of Vincent's infection supplements Rosebury's chapter quite ably. The chapter on selected diseases of the mouth by Cornbleet could be better organized and more up-to-date. We have never seen malignant epulides and do not believe that mixed tumors are prone to become malignant. Dean's contribution on chronic dental fluorosis omits the results of animal experimentation. Lyons could have done better on the subject of the pulpless tooth and factors concerning its therapy. A discussion of contraindications to the treatment of pulpless teeth should not have been omitted. The properties of restorative materials are discussed by Peyton. Seevers writes a review on the principles of inhalation anesthesia; Tuoty on its clinical aspects in dentistry; Tainter and Moose on local anesthesia. These three chapters give an informative and complete survey of the field. Antiseptics and disinfectants are handled by Hull, who treats of their physical and chemical properties and dwells at some length on the phenol coefficient and other tests for disinfectants. The chapter on statistical methods in dentistry by Gafafer should be helpful in eliminating to some extent the contradictory conclusions frequently recorded in professional journals. H. C.

THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE THYROID. By JAMES H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University and Chief of the Medical Services, Massachusetts General Hospital, and EDWARD P. RICHARDSON, M.D., John Homans Professor of Surgery, Harvard University, and Chief of the West Surgical Service (Massachusetts General Hospital). (Reprinted from Oxford Monographs on Diagnosis and Treatment.) Pp. 367; 51 illustrations. New York: Oxford University Press, 1938. Price, $5.00.

THIS is a revision, separately reprinted, of a monograph which originally appeared in the Oxford Monographs on Diagnosis and Treatment in 1929. The authors are well known for their contributions to the medical and surgical aspects, respectively, of thyroid disease. The volume represents a clear, but not too detailed, review of the more important clinical aspects of thyroid disease, with emphasis upon the practical problems. The value of the work is enhanced by judiciously selected case histories. Although it lacks somewhat the flavor and discursive style of the senior author's excellent book on the Thyroid and Its Diseases, it can be recommended for the practitioner or student who wishes to keep abreast of the soundest current thought in its field. E. R.

CONSOLIDATED INDICES. Embracing Transactions of the American Roentgen Ray Society (1903–1908); American Quarterly of Roentgenology, Vols. I–V (1906–1913); American Journal of Roentgenology, Vols. I–IX (1913–1922); American Journal of Roentgenology and Radium Therapy, Vols. X–XXXVIII (1923–1937). Author and Subject: 1903–1937. Compiled under the direction of the Publication Committee and the Editorial Office of the American Roentgen Ray Society, 1939. Pp. 451. Springfield, Ill.: Charles C Thomas, 1939. Price, $12.50.

THIS book has been compiled under the direction of the Publication Committee and the Editorial Office of the American Roentgen Ray Society, who are to be congratulated on their service to medicine. The work has been prepared by a real authority and should be of great assistance to any one looking up the subjects in radiology, especially in the early periods before comprehensive indices were available. The entire work has been done in a most meticulous manner. E. P.

CLINICAL BACTERIOLOGY. By F. A. KNOTT, M.D., M.R.C.P., D.P.H., Director, Bacteriological Department, and Lecturer in Bacteriology, Guy's Hospital. Pp. 426; 60 illustrations, including 12 plates. Philadelphia: P. Blakiston's Sons & Co., Inc., 1939. Price, $4.50.

THE author's attempt to present the clinical significance of bacteriologic phenomena has not, in the Reviewer's estimation, been successful. The book is too incomplete for use as a textbook; it will be of little use to clinical pathologists because of the lack of laboratory procedures; and it offers nothing to clinicians which they can not obtain from any good textbook of medical bacteriology. Its value is further reduced because of an absence of bibliography. Inconsistencies and errors appear through the book, too numerous to detail here. [The Reviewer gave some 8 or 10 examples by way of illustration, but they have been deleted to save space. EDITOR.]

The contents of the book possess nothing for which it can be recommended in this country. H. M.

STUDIES OF TRAUMA AND CARBOHYDRATE METABOLISM WITH SPECIAL REFERENCE TO THE EXISTENCE OF TRAUMATIC DIABETES. By VIGGO THOMSEN. Pp. 416; illustrated. Copenhagen: Ejnar Munksgaard, 1938. Price, d. Kr. 15.

THE opening account of the general history of trauma as related to diabetes affords a clear, well documented background of the medical and legal problems which have arisen when trauma has preceded the discovery of glycosuria. The author's work includes various studies of the blood and urine sugar in 144 injured normal persons and case reports of 100 injured diabetics. He also summarizes 81 case reports of so-called traumatic diabetes from the literature. There is a chapter on his investigations concerning the mechanism of post-traumatic disturbances in man. He regards overactivity of the sympathetic nervous system as the cause of the hyperglycemia. Some of the patients were tested for their tolerance to glucose with and without ergotamine in an effort to demonstrate this point; the author rightly regards these results as inconclusive. In a judicious summary, the conclusion is reached that except for the theoretic case of pancreatic injury, trauma cannot cause diabetes nor can it cause more than a temporary exacerbation of an existing diabetes.

There are some minor typographical errors, but the book combines a sound appraisal of the problem with good original clinical observations which combine to make one respect the author's opinion. Physicians, surgeons and those concerned with forensic medicine will find this a valuable reference work. F. L.

STUDIES ON THE SIZE OF THE RED BLOOD CELLS ESPECIALLY IN SOME ANAEMIAS. By ERIK MOGENSEN. Pp. 216; 43 illustrations. Copenhagen: Ejnar Munksgaard; London: Oxford University Press, 1938.

THE size of the red blood cells—both volume and diameter—has become of greatly increased clinical importance in the past decade, since it was recognized that it was a valuable measurement both in the diagnosis and control of treatment in various anemias. Following a description of the various techniques—especially the Price-Jones curves, the author has analyzed the studies by himself and others in health and disease. Thus he finds that the average mean diameter of normal human red cells is 7.15 μ (Stand. dev., 0.46 μ) and that in untreated pernicious anemia the cell population can be split into two more characteristic size groups. The effects of lack of iron in pernicious anemia, cancer, and so on as well as in simple hypochromic anemia, are analyzed. Without settling anemia problems, this book is a sound objective contribution to an active phase of anemia study

E. K.

THE FUNCTIONS OF HUMAN VOLUNTARY MUSCLES. By NORMAN D. ROYLE, M.D., CH.M., F.R.A.C.S., Honorary Demonstrator of Anatomy, University of Sydney; Senior Orthopedic Surgeon, Lewisham Hospital, Sydney, etc. Pp. 42; 11 illustrations. Sydney: Angus & Robertson Ltd., 1938. Price, 3/6.

THE author collaborated with J. I. Hunter in his work on the sympathetic innervation of voluntary muscles in 1934. Professor Burkitt in his foreword recounts that the author's interest in muscles began in his student days, and this interest extended to his personally developing considerable control of individual muscles. With such a background it is not surprising that this little volume contains much of practical value and much that is omitted from the more academic expositions. Its simplicity and directness is apparently the result of complete familiarity with the field. A beginning medical student could read it with enjoyment and the practitioner or specialist in anatomy or orthopedics could read it with profit. O. B.

INSULIN. Its Chemistry and Physiology. By HANS F. JENSEN, PH.D., Associate, Laboratory for Endocrine Research, The Johns Hopkins University, Pp. 252. New York: The Commonwealth Fund, 1938. Price, $2.00.

IT is fitting that a monograph upon the structure and properties of insulin should emanate from the laboratory of the late Professor Abel of Hopkins who in 1922 isolated this hormone. Dr. Jensen's monograph is timely and of great value. G. W.

SYNOPSIS OF PULMONARY TUBERCULOSIS. By JACOB SEGAL, M.D., Physician in Charge of Fordham Hospital Tuberculosis Clinic, New York; Associate Visiting Physician, Riverside Hospital, New York, and Bronx Hospital. Foreword by the late POL N. CORYLLOS, M.D., F.A.C.S., Professor of Clinical Surgery, Cornell Medical College; Director of Thoracic Surgery at Seaview and Metropolitan Hospitals, New York, etc. Pp. 150; 21 illustrations. New York: Oxford University Press, 1939. Price, $2.75.

IN this small volume a difficult task has been accomplished creditably. The author has attempted to condense in very limited space the accepted facts on tuberculosis as respects its pathogenesis, clinical types, diagnosis,

complications, treatment and prevention. By excluding controversial subjects he has been able to present a reasonably well rounded picture to which little exception can be taken. Obviously this small monograph is not a reference book, but it is useful for beginners in tuberculosis, and particularly for those not intending to specialize in the disease, but anxious to be brought up to date in the field. The book is copiously illustrated with reproductions of Roentgen ray films. The style is simple, if at times colloquial; the meaning is always clear. A foreword by the late Dr. Pol N. Coryllos is prefixed to the text. E. L.

THE WISDOM OF THE BODY. By WALTER B. CANNON, M.D., Sc.D., LL.D., DR. (HON.), George Higginson Professor of Physiology, Harvard Medical School. Pp. 333; 40 illustrations. New York: W. W. Norton & Co., Inc., 1939. Price, $3.50.

THE valuable account of the means utilized to maintain constant conditions in the body (homeostasis), which Dr. Cannon gave in 1932 has been reprinted with some modifications and additions. In general the form remains the same with its lucid expression of physiologic facts in terms mostly understandable by the layman. The additional material mainly deals with the effects of age on such adaptations and a comparison of the capacities of the dog and cat to adjust to difficult conditions. As in the original volume the evidence is mainly drawn from the brilliant series of researches of Dr. Cannon and his co-workers. H. B.

SURGICAL TREATMENT OF HAND AND FOREARM INFECTIONS. By A. C. J. BRICKEL, A.B., M.D., Departments of Anatomy and Surgery, Western Reserve University. Pp. 300; 166 illustrations and 35 plates (10 in color). St. Louis: The C. V. Mosby Company, 1939. Price, $7.50.

HERE is an authoritative monograph: well written and beautifully illustrated. The basic work of Kanavel, on infections of the hand, has been greatly supplemented and advanced. The section on surgical treatment is excellent. G. W.

CLINICAL GASTRO-ENTEROLOGY. By HORACE WENDELL SOPER, M.D., F.A.C.P., Pp. 314; 212 illustrations. St Louis: The C. V. Mosby Company, 1939. Price, $6.00.

DR. SOPER'S work is short, to the point, and very readable. It is, however, rather a condensation of personal impressions, chiefly on therapy, than a didactic presentation of the diseases of the digestive tract. Many sections, such as those on peptic ulcer, intestinal obstruction, hepatic and biliary disease are rather sketchy. The only liver disease described, for instance, is tænia echinococcus infestation. The best feature of the book is the large number of excellent Roentgen ray photographs. The general practitioner will find many interesting therapeutic and dietary suggestions, especially on diseases of the colon. Specialists will insist on a more complete coverage of the field of gastro-enterology. J. D.

CONSULTATION ROOM. By FREDERIC LOOMIS, M.D., Diplomate of the American Board of Obstetrics and Gynecology. Pp. 281. New York: Alfred A. Knopf, 1939. Price, $2.50.

ONE begins reading this book to find, if one is a physician, a rather commonplace account of the circumstances surrounding a youth who *knew* he wanted to be a physician and of the various difficulties to be overcome. To the laity, however, these opening chapters will doubtless have more interest and color. Established as an obstetrician-gynecologist, the author has

stories to tell—dramatic human problems naturally revolving about sex—that will arouse and captivate the interest of the layman and the human physician alike. The problems of pain and death, honor and spiritual distress, selected from the thousands of cases that the author has seen in the many years of his special practice on the Pacific Coast, are described in a simple, yet fresh and vigorous style. Little is said directly about the author's private life, though his personality emerges distinctly as the tale proceeds. In the latter half of the book, which has long since "sold" itself to the reader, much sound information on what every woman should know is skillfully and innocuously interlarded with the illustrative incidents that fill the text. Few woman readers, and few mere males, too, for that matter, will fail to be charmed and instructed by this unusual book. E. K.

THE PRINCIPLES AND PRACTICE OF OPHTHALMIC SURGERY. By EDMUND B. SPAETH, M.D., Associate Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania; Ophthalmologist to the Orthopedic Hospital and Infirmary for Nervous Diseases, Philadelphia; Consultant in Ophthalmology to the Philadelphia Hospital for the Insane (Byberry), etc. Pp. 835; 413 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $10.00.

This book is unquestionably the best in the English language on ophthalmic surgery. It covers the entire field from plastic surgery of the lids to all forms of operations on the globe. The illustrations are excellent and the descriptions of the operative procedures are clear and concise. It cannot be too highly recommended. F. A.

PULMONARY TUBERCULOSIS IN ADULTS AND CHILDREN. By JAMES ALEXANDER MILLER, A.M., M.D., D.P.H., Sc.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; late chief of, now Honorary Consultant to, the Tuberculosis Service, Bellevue Hospital, New York, and ARVID WALLGREN, M.D., Head of the Children's Hospital, Gothenburg, Sweden. Pp. 196; 77 illustrations. New York: Thomas Nelson & Sons, 1939. Price, $3.50.

THIS book consists of a modification of separate sections recently contributed by Dr. Miller and Dr. Wallgren to the Nelson Loose Leaf Medicine. It is interesting that two authors, widely separated geographically, have found their views so compatible in the related fields of tuberculosis in adults and in children as to warrant a joint publication. Both are well known to American readers, Miller for his writings in the general field of tuberculosis and particularly hematogenous tuberculosis, and Wallgren for his studies on primary tuberculosis. Miller's section of the present volume covers infection and the pathogenesis, clinical course, diagnosis and treatment of tuberculosis as it occurs in adults; while Wallgren's section is devoted to the pathogenesis and clinical course of the disease, not merely as it occurs in children, but as it is seen in primary form in adolescents.

Neither section is a mere review of accepted facts; each is distinctly individualistic, representing views championed particularly by its author. Miller is definitely committed to the view that tuberculosis of the adult represents endogenous infection almost exclusively. His statement that this is the contested, however, by many students of the disease. He follows the "trigger hypothesis" of Redeker in explaining the cases apparently resulting from view of the majority of clinicians and pathologists today would probably be contact with open disease. He divides tuberculosis into non-phthisical,

prephthisical and phthisical forms, and subdivides the latter into early, established and terminal pneumonic phthisis. As an advocate for the theory of endogenous onset of adult tuberculosis, he adopts the view that "there is no such thing as clinically definite incipiency of pulmonary tuberculosis." The process is a continuous story, if not one of uniform speed. The various types of tuberculosis, which are well recognized by tuberculosis specialists in general under varying designation, are abundantly illustrated by excellent reproductions of Roentgen ray films. The section devoted to treatment is concise and practical, with the lines clearly drawn for management of cases of the different types and their various complications.

Wallgren's section is notable for its consideration of the clinical character of primary tuberculosis, a subject of much renewed interest in view of the world-wide postponement of first infection tuberculosis and the accompanying general diminishing mortality. Numerous case reports are included, and the relations to allergy and the development and waning of tuberculin sensitiveness are particularly stressed. Like Miller, Wallgren adopts the view of endogenous exacerbations as the cause of post-primary manifestations of tuberculosis. He is also a vigorous proponent of the importance of constitutional factors in resistance. His thesis of the genesis of the tuberculosis of adult life is concisely stated as follows: "A combination of a good natural resistance and the absence of unfavorable factors will prevent the occurrence of consumption. A combination of an inherited low resistance and unfavorable factors is almost inevitably bound to lead to phthisis."

All interested in tuberculosis will find the book stimulating and informative.

E. L.

NEW BOOKS.

The Genuine Works of Hippocrates. Translated from the Greek by FRANCIS ADAMS, LL.D., Surgeon. With an Introduction by EMERSON CROSBY KELLY, M.D. Pp. 384; 8 plates. Baltimore: The Williams & Wilkins Company, 1939. Price, $3.00.

The Physiology and Pharmacology of the Pituitary Body. Vol. II. By H. B. VAN DYKE, Head of the Division of Pharmacology, Squibb Institute for Medical Research, New Brunswick, N. J.; Honorary Professor of Physiology, Rutgers University, etc. Pp. 402; 28 illustrations. Chicago: The University of Chicago Press, 1939. Price, $4.50.

Physiology of the Uterus. With Clinical Correlations. By SAMUEL R. M. REYNOLDS, M.A., PH.D., Fellow, John Simon Guggenheim Memorial Foundation, The University of Rochester School of Medicine and Dentistry, Rochester, N. Y.; Associate Professor of Physiology, Long Island College of Medicine, Brooklyn, N. Y. With Forewords by GEORGE W. CORNER, M.D., Professor of Anatomy, University of Rochester School of Medicine and Dentistry, Rochester, and ROBERT T. FRANK, M.D., F.A.C.S., Consulting Gynecologist, Mt. Sinai Hospital, New York; Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University, New York. Pp. 447; 44 illustrations. New York: Paul B. Hoeber, Inc., 1939. Price, $7.50.

Enrico Bottini and Joseph Lister in the Method of Antisepsis. Pioneers of Antiseptic Era. By G. P. ARCIERI. (Reprint from Alcmeone, Vol. 1, No. 1, 1939.) Pp. 40; 1 illustration. New York: Franco Frusci, 1939.

The Patient as a Person. A Study of the Social Aspects of Illness. By G. CANBY ROBINSON, M.D., LL.D., Sc.D., Lecturer in Medicine, Johns Hopkins University. Pp. 423. New York: The Commonwealth Fund, 1939. Price, $3.00.

Fever and Psychoses. A Study of the Literature and Current Opinion on the Effects of Fever on Certain Psychoses and Epilepsy. By GLADYS C. TERRY, Research Associate in Neurology, Neurological Institute of New York, Columbia University; Formerly Research Assistant in Psychiatry, Henry Phipps Clinic, Johns Hopkins University. Pp. 167. New York: Paul B. Hoeber, Inc., 1939. Price, $3.00.

Clinical Pathological Gynecology. By J. THORNWELL WITHERSPOON, B.S. (Princeton), B.A., and M.A. (Oxon.), M.D. (Johns Hopkins), Formerly Associate Professor of Experimental and Pathological Gynecology, Indiana University Medical Center, Indianapolis. Pp. 400; 271 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $6.50.

Studies on the *Changing Incidence of Peptic Ulcer* of the Stomach and Duodenum. By GUNNAR ALSTED, M.D., Privat-docent at the University of Copenhagen; Assistant Physician and Member of the Staff, Bispebjerg Hospital, Copenhagen. With a Preface by PROFESSOR E. MEULENGRACHT. Pp. 148; 12 illustrations. Copenhagen: Ejnar Munksgaard, 1939. Price, Sh. 10/

End Results in the Treatment of Gastric Cancer. An Analytical Study and Statistical Survey of Sixty Years of Surgical Treatment. By EDWARD M. LIVINGSTON, B.Sc., M.D., Associate Visiting Surgeon, Bellevue Hospital, New York; Assistant Clinical Professor of Surgery, New York Unisity College of Medicine, etc., and GEORGE T. PACK, B.Sc., M.D., F.A.C.S., Attending Surgeon, Memorial Hospital, New York City; Assistant Professor of Clinical Surgery, The School of Medicine, Yale University, New Haven, and Cornell University Medical College, New York City. With a Foreword by BOWMAN C. CROWELL, M.D., Associate Director, American College of Surgeons. Pp. 179; illustrated. New York: Paul B. Hoeber, Inc., 1939. Price, $3.00.

What it Means to be a Doctor. By DWIGHT ANDERSON. Pp. 87. New York: Medical Society of the State of New York, 1939. Price, $1.00.

Vignettes of fictitious doctors aimed to give the prospective physician and the public better knowledge of what a physician's life consists of. Sponsored by the Medical Society of the State of New York and based on a questionnaire sent to 500 physicians in various fields, asking four questions calculated to illuminate the subject.

Le Radon en Thérapeutique. By DOCTEUR P. E. MORHARDT. Pp. 19. Paris: Édité Par Les Laboratoires Virac, 1939.

Rural Medicine. Proceedings of the Conference Held at Cooperstown, New York, October 7 and 8, 1938. Pp. 268; 15 illustrations, 13 tables and 35 charts. Springfield, Ill.: Charles C Thomas, 1939. Price, $3.50.

Proceedings of the American Philosophical Society for Promoting Useful Knowledge, held at Philadelphia (Vol. 80, No. 3, Feb. 10, 1939). Contents: Measles and Scarlet Fever in Providence, R. I., 1929–1934, with Respect to Age and Size of Family. By EDWIN B. WILSON, CONSTANCE BENNETT, MARGARET ALLEN and JANE WORCESTER, Harvard School of Public Health. Pp. 120; illustrated. Philadelphia: The American Philosophical Society, 1939. Price, 75c.

The Medical Clinics of North America, Vol. 23, No. 3 (New York Number, May, 1939). Pp. 277; 30 illustrations. Philadelphia: W. B. Saunders Company, 1939.

Physiological Differentiation in Lymnaea Columella. By JOSHUA L. BAILY, JR. With a Foreword by RAYMOND PEARL (The American Journal of Hygiene, Monographic Series, No. 14, April, 1939). Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 133; illustrated. Baltimore: The Johns Hopkins Press, 1939. Price, $1.00.

Life and Letters of Dr. William Beaumont. By JESSE S. MYER, A.B., M.D., Late Associate in Medicine in Washington University, St. Louis. With an Introduction by SIR WILLIAM OSLER, BT., M.D., F.R.S., Late Regius Professor of Medicine in Oxford University, England. Pp. 327; illustrated. St. Louis: The C. V. Mosby Company, 1939. Price, $5.00.

Heart Patients. Their Study and Care. By S. CALVIN SMITH, M.D., Sc.D., Formerly Special Heart Examiner for the Surgeon General's Office during the World War at home and abroad. Pp. 166. Philadelphia: Lea & Febiger, 1939. Price, $2.00.

Problems in Prison Psychiatry. By J. G. WILSON, M.D., Senior Surgeon (Retired), United States Public Health Service; Director, Division of Hospitals and Mental Hygiene, Department of Health of the State of Kentucky, and M. J. PESCOR, M.D., Clinical Director, United States Public Health Service Hospital, Fort Worth, Texas. Pp. 275. Caldwell, Idaho: The Caxton Printer, Ltd., 1939. Price, $3.00.

The New International Clinics, Vol. 2, N. S. 2, June, 1939. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa. With 17 Collaborators. Pp. 321; many illustrations and 1 colored plate. Philadelphia: J. B. Lippincott Company, 1939.

This number includes several articles of important present interest such as Musser's Pellagra; Wilder's Diabetic Arteriosclerosis; Neurologic (Clough) and Psychiatric (E. L. Richards) Aspects of Vitamin Deficiencies; Choice of Methods for the Correction of Anemia (Wintrobe). There are 6 "Clinics" and a Review of Peroral Endoscopy by L. H. Clerf.

NEW EDITIONS.

Sex and Internal Secretions. A Survey of Recent Research. Editor: EDGAR ALLEN, Yale University. Associate Editors: CHARLES H. DANFORTH, Stanford University, and EDWARD A. DOISY, St. Louis University. Twenty-seven Contributors. With Forewords by ROBERT M. YERKES, Yale University. Pp. 1346; 454 illustrations, 2 color plates, and numerous tables. Second edition, enlarged and revised. Baltimore: The Williams & Wilkins Company, 1939. Price, $12.00.

Recent Advances in Medicine. By G. E. BEAUMONT, M.A., D.M. (OXON.), F.R.C.P., D.P.H. (LOND.), Physician to the Middlesex Hospital; Physician to the Hospital for Consumption and Diseases of the Chest, Brompton; Lecturer in Medicine, Middlesex Hospital Medical School, etc., and E. C. DODDS, M.V.O., D.Sc., PH.D., M.D., F.R.C.P., Courtauld Professor of Biochemistry in the University of London; Director of Courtauld Institute of Biochemistry, Middlesex Hospital; Pathologist to the Royal National Orthopaedic Hospital. Pp. 431; 42 illustrations. Ninth Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, $5.00.

Food and Health. An Introduction to the Science of Nutrition. By A. BARBARA CALLOW, M.A. (CANTAB.), M.Sc. (LOND.), M.S. (YALE). Pp. 168; illustrated. Second Edition. New York: Oxford University Press, 1938. Price, $1.75.

Textbook of General Surgery. By WARREN H. COLE, M.D., F.A.C.S., Professor of Surgery, University of Illinois College of Medicine, etc., and ROBERT ELMAN, M.D., Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Pp. 1031; 559 illustrations. Second Edition. New York: D. Appleton-Century Company, Inc., 1939. Price, $8.00.

Laboratory Manual of the Massachusetts General Hospital. By FRANCIS T. HUNTER, M.D. Pp. 119. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, $1.75.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE.

UNDER THE CHARGE OF
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ADDISON'S DISEASE.

ALMOST 300 years passed from the time Eustachius discovered the adrenal glands in 1563 until Addison described the disease which now bears his name in 1849,[1a] and again in 1855.[1b] In the 75 years following Addison's description increasing recognition of the disease continued, but only in the past 10 years has the fundamental nature of the mechanisms involved in the symptom-complex begun to become apparent. Truly Addison's wish is in the process of being fulfilled, "I cannot but indulge the hope, that by attracting the attention and enlisting the co-operation of the Profession at large, they (the facts) may lead to the subject being properly examined and sifted, and the inquiry so extended, as to suggest, at least, some interesting physiological speculations, if not still more important practical indications." The literature on this subject has become so voluminous that only certain recent aspects of clinical interest find room for review here. Much of additional interest will be found in the Symposia on Quantitative Biology of the Cold Spring Harbor for 1937,[32] where cortical hormones are discussed by many eminent authorities.

Etiology. The original description of Addison's disease rested upon the basis of tuberculosis of the adrenal gland. Subsequent reports have indicated that as high as 90% of Addison's disease patients have tuberculosis of this organ, and considerable variation in this value has been reported. Guttman,[27] in his survey of the literature in 1930, found the causes in 566 cases to be tuberculosis in 69.72%, atrophy in 19.38%, amyloid in 1.73%, neoplasm in 1.24%. The remaining 7.83% were divided among such diagnoses as hemorrhage, syphilis, pressure atrophy, fatty degeneration, venous thrombosis, and arterial emboli.

Less than one-half of those with Addison's disease due to tuberculosis show associated tuberculosis elsewhere,[62a] and until recently such complicating lesions have been shown to have little effect on the course of the disease. The lungs are the focus in approximately 50% and hidden or active foci in other parts of the body in the remainder. Tuberculosis of the adrenals is hematogenous and secondary to tuberculosis elsewhere.

The incidence of Addison's disease is surprisingly low in sanatorium patients. In 15 years one group[13] found only 2 cases in 4500 patients. The explanation is questionable, but probably involves many factors. Extensive bilateral tuberculosis of the adrenal glands is usually seen in cases with minimal or healed pulmonary tuberculosis. Furthermore, extensive disease of the adrenal glands often appears after dismissal from sanatorium care. It must be remembered, too, that pulmonary tuberculosis may mask Addison's disease, for it may produce similar symptoms. Still, under these circumstances Bronfin and Guttman have shown that the diagnosis may be made when asthenia, loss of weight, anorexia, and abdominal distress are out of proportion to the extent or activity of the pulmonary lesions.

Sex distribution in tuberculous Addison's disease has varied from equal values to an incidence favoring males. Age incidence follows closely the death age distribution of tuberculosis in general. It is uncommon in childhood,[22] only from 1 % to approximately 3.5 % of the cases occurring in this period.

Tuberculosis of the adrenal glands is not always accompanied by Addison's disease, even when bilateral. Colton[15] found only 6 cases of Addison's disease in 14 patients with bilateral tuberculous adrenals.

Next to tuberculosis, atrophy is the most frequent cause of Addison's disease, and its incidence appears to be increasing.[69] Of 18 patients with Addison's disease, 11 were found to be due to tuberculosis and 7 to atrophy. Susman, in his review of 11 reports from various countries, found support of these figures in certain geographical areas. Highest incidence of atrophy occurred in the English group. Of the 189 cases of Addison's disease, 96 (51 %) were from England. Thirty-two (70 %) of 46 instances of atrophy were in the English group, an incidence of 33 % among the English cases. American reports, too, continue to show an increased incidence of atrophy. Von Glahn[77] saw, from 1926 to 1935, 5 instances of atrophy, while in 24 years previously he had seen only 6 cases, all due to tuberculosis. Barker,[7] in 1929, reported 28 cases, 25 due to tuberculosis and 3 to atrophy. Robertson[55] indicated that since Barker's paper, 19 cases were observed, 9 (approximately $\frac{1}{2}$) due to atrophy.

Atrophy, unlike tuberculosis, has been more frequent in females,[69] and it, too, has been found in children. (It is rare in childhood.[5,22,39,64] Atkinson has reviewed the subject thoroughly and has collected all reported cases of all types.) The usual age incidence is between 25 and 60 years, and the general incidence in available autopsy series varies from 0.025 to 0.29 %.

The etiology of so-called atrophy is still a mystery, despite the many, and often divergent, views offered as an explanation.[11] A partial list of suggestions includes congenital hypoplasia, endocrine factors, chronic inflammations (such as lues, tuberculosis, and non-specific inflammations), circulating cytotoxins, and simple atrophy. These many explanations have led to a number of different names being applied to the condition,[78] such as simple atrophy (Karakaschaff), idiopathic atrophy (Simmonds), inflammatory granular atrophy (Rössle), cytotoxic contracted suprarenal gland (Kovacs), and chronic idiopathic (primary) suprarenal insufficiency (Bittorf).

In atrophy, as well as in tuberculosis, much controversy has arisen in the past concerning the place and importance of the medulla in the etiology of the clinical picture. Recent work, including substitution therapy in animals and man, indicates the prime importance of the cortex, but does not deny that medullary changes may contribute to the clinical picture in any one patient.

Endocrine influences from glands other than the adrenal have enjoyed considerable popularity as an explanation of the etiology of atrophy, particularly since interrelationships of endocrine glands, including the adrenal, have been definitely accepted. Chief interest centers around the thyroid and the pituitary. The problem of the participation of the thyroid has prompted spirited debate in the German literature,[78] for the thyroid quite frequently shows lymphocytic infiltration which may become very extensive. The significance of this change is unknown. While evidence of hyperactivity of the thyroid is found in some cases, it is not a constant finding.[16]

Recently the pituitary has received much attention in relationship to Addison's disease. Nicholson[51] autopsied 25 adrenalectomized dogs and compared the anterior pituitary with the glands of normal animals. He was unable to find histologic differences. In sections from 7 pituitaries from human Addison's disease, there was a reduction in the number of basophils, along with abnormal basophilic cells only in those patients with adrenal cortical atrophy. From such findings he suggested that Addison's disease due to atrophy begins primarily in the anterior lobe of the pituitary, and that the absence of adrenotropic hormone causes adrenal cortical atrophy which, in turn, is responsible for the clinical picture of Addison's disease.

The work of others does not warrant such suggestions. In 1935 Crooke and Russell[16] pointed out that in 9 of 13 published examinations of the pituitary gland in Addison's disease a diminution of basophilic cells is described. A great reduction of basophilic cells was constant in their series of 12 cases, whether or not the adrenals were tuberculous or atrophied, a factor against Nicholson's view. They found large chromophobe cells, a decrease in the number of acidophils, and a number of abnormal transitional basophils, with a constant striking reduction in the number of ripe basophils. In 5 glands the findings were checked by Rasmussen's method. The abnormal basophilic cells were more numerous than the ripe basophils, but both groups together were below the minimum for ripe basophilic cells in Rasmussen's series, except in one case.

Discussing these observations, the authors recall that basophilic adenomata of the pituitary are frequently accompanied by diffuse hypertophy of the adrenal cortex, the opposite findings of Addison's disease. Likewise, destruction of the anterior lobe of the pituitary[54,61] is followed by adrenal cortical atrophy. Such atrophy is not associated with cellular infiltration or fibrosis. Atrophy of Addison's disease is not simple atrophy but a destruction of the parenchyma similar to that of acute atrophy of the liver, and areas where cells disappear are infiltrated with large and small lymphocytes, plasma cells, and monocytes. The remaining cortical cells show changes in staining reaction, are hypertrophied and are grouped. Later fibrosis appears. These authors, therefore, consider the atrophy of Addison's disease a destructive

atrophy, differing from that secondary to pituitary hypofunction. The diminution in basophils may be secondary to it, for although Nicholson found no differences in adrenalectomized dogs, others[50] have found definite changes in rats.

Bloch[10] has advanced the theory that atrophy is not true atrophy but the result of a perversion of the normal process of development of the medulla during fetal life. Normally the embryonic neurocytes, which migrate through the cortex, eventually form the medulla. With the increase in size of the medulla there is a corresponding atrophy of the cortical inner zone with a regeneration of the glomerular zone. Bloch thinks, if the process of atrophy of the inner zone is prolonged into early childhood or later life, the great bulk of the cortex may eventually disappear, having been replaced by embryonic neurocytes. This theory has received little support.

Other possibilities have been considered in the cause of cortical necrosis. Wells, Humphreys and Work[79] have noted in the cortical lesions histologic features similar to those of cinchophen poisoning in the liver. This, together with the similarity of the appearance of both diseases in hospitals during recent years, aroused their suspicions that the selective destruction might have been produced by some drug or other chemical agent. Microscopic lesions in the necrotic adrenal cortex of a patient who had taken germanin were similar to those seen in Addison's disease. The picture was reproduced in animals. However, this chemical has not been related to cortical atrophy in patients with Addison's disease. The report merely indicates, indirectly, that drugs may be responsible for the atrophic cortex in human Addison's disease, without offering any confirmation of this hypothesis.

Less common causes of Addison's disease continue to be reported and new and unusual associations with Addison's disease appear to be limited only by the number of conditions capable of causing sufficient cortical dysfunction. For example, a French report[41] describes Addison's disease secondary to a destructive lesion of the splanchnic medullary centers. Somewhat similar is Rogoff's patient,[56b] who suffered from diabetes mellitus. An attempt was made to benefit the diabetes by denervation of the adrenals. Both sides were denervated, but at different times. Addison's disease developed, the surgical manipulations apparently resulting in occlusion of blood-vessels and degeneration of the adrenal cortex. The latter inference is based upon animal studies in which creation of serious local circulatory disturbances produced acute and chronic adrenal cortical insufficiency.[56a] Snell, Wilder and Cragg[63] have reported a similar case with adrenal atrophy following denervation resulting in a typical clinical picture of Addison's disease. This complication of adrenal surgery must be rare, however, when one considers the frequency of such surgery and the rarity of reports of the development of Addison's disease.

Tuberculosis may be an indirect as well as a direct cause of Addison's disease by the production of amyloid degeneration. Such changes are not frequent. Guttman[27] found an incidence of only 1.26%. Yet amyloid is found in the adrenals, if sought, in many cases of amyloidosis of the spleen and other organs. For example, in 100 patients with tuberculosis, 18 instances of amyloidosis were found, 14 of which (78%) showed amyloid in the adrenals.[13] The suggestion was made that at

least 3 possibilities may account for the differences in the incidence of amyloidosis of the adrenal and Addison's disease due to amyloidosis; namely, insufficient destruction of cortex, prevention of Addison's disease by the medulla, and masking of the symptoms by pulmonary tuberculosis. The effect of the medulla is questionable for it is well preserved. Cortical tissue is preserved in amyloidosis of the adrenals and islands of tissue appear normal histologically. In Bronfin and Guttman's 14 cases, histologic changes in the adrenal seemed to show a relationship between the extent of the amyloid of the cortex and the symptoms. They also call attention to the possibility that in advanced pulmonary tuberculosis there are symptoms of Addison's disease which are usually unrecognized and attributed to existing tuberculosis.

Weiner[78] described a patient with nuclear inclusions in the adrenal cortical tissues but not in the other tissues sectioned nor in many adrenals of varied diseases. Aside from the nuclear inclusion bodies the findings in this patient fit other descriptions of atrophy.

Addison's disease occurs at times in association with other diseases, and frequently attempts are made to show interrelationships and common etiologic factors. For example, pellagra has occurred with Addison's disease.[59] Attention has been called to the similarity of the pigmentary phenomena in the 2 diseases. Similarly, Addison's disease has been reported in a patient with Buerger's disease.[60] No causative relationships between the 2 conditions were established, and the possibility of adrenal atrophy resulting from circulatory changes due to the Buerger's disease was discarded as unlikely in this patient. Addison's disease has also been reported in association with mycosis fungoides.[4]

Attempts have been made to show hereditary factors in Addison's disease. At present such associations seem unimportant. Familial occurrence of acromegaly and Addison's disease has been reported,[47] and the disease is usually considered less frequent in the negro. Flippin and Smith[20] brought this out strikingly in their report. They point out that since Addison's disease occurs more frequently in the laboring class, and since tuberculosis is very frequent in the negro, one would expect a high incidence of Addison's disease in this group. Yet it is very infrequently reported in the negro, though it is probably more frequent than is generally appreciated. The normal pigmentation of the negro may be a factor in the failure of its recognition, although in 14 reported cases there were 12 with increasing pigmentation recognized by the patients or their friends.

Clinical Aspects. Only certain aspects of the clinical expressions of Addison's disease will be considered here. The usual course of the clinical findings, pigmentation, asthenia, blood pressure variations, gastrointestinal and other well known changes will be passed over without comment. The average duration of symptoms, and life, is said to be 1 to 3 years, longer with atrophy than with tuberculosis, and longer with marked pigmentation than without it. Of chief importance is the division of these symptoms and signs into 2 groups, one the chronic findings, such as slight asthenia, pigmentation, symptoms of hypoglycemia and hypotension; the other the findings of crisis, such as anorexia, nausea and vomiting, diarrhea, and circulatory collapse. This classification is similar to that used in diabetes mellitus and exophthalmic goiter.

Since the clinical picture results from an insufficient supply of cortical

hormone or hormones, recitation of the clinical aspects is essentially an exposition of the functions of the cortical hormones, and, to quote Loeb,[43b] until it is available in large amounts in crystalline form, the functions will remain shrouded in mystery and confusion. A discussion of the hormones, other than cortin, may be found in the report of Hartman.[32] Recent production of synthetic preparations having the life sustaining activity of cortical extract[67] indicates that we may be on the verge of a clarification of this problem.

Changes in carbohydrate metabolism have been noted both in patients and in experimental animals. Removal of the adrenal glands in animals and the development of Addison's disease in certain patients results in a decreased blood sugar and an increased sensitivity to insulin. Adrenalectomized animals with resulting adrenal insufficiency have been shown to have a reduced liver glycogen and a low blood sugar[12b] and have lost the ability to form liver glycogen from injected glucose. Welty and Robertson[80] have recently reviewed the clinical aspects of hypoglycemia.

Hypoglycemia has not been found in all patients with Addison's disease. In some it may be marked, however, producing coma. For example, Anderson and Lyall's patient[3] died in coma with hypoglycemia while plasma chlorides and blood urea were both within normal limits. It has been attributed to disturbances of cortical function,[12a,b] to possible deficiency of basophilic cells in the anterior pituitary[16] and also to destruction of the medulla with a disturbance in the balance between insulin and adrenalin. There is evidence[14] that blood adrenalin is lowered in Addison's disease, a sign thought by certain European investigators to be of value in atypical and abortive cases. Further evidence for medullary involvement is the demonstration by Harrop and Weinstein[29] that insulin sensitivity persists in adrenalectomized dogs with adequate dosage of cortical extract. Varying involvement of the medulla would explain the presence of hypoglycemia in some patients and its absence in others. Still there may be more than a single mechanism, for Althausen, Anderson and Stockholm[2] have recently demonstrated a reduced absorption of glucose from the intestine, corrected by salt therapy, in experimental adrenal insufficiency. Possibly both the medulla and cortex play a part in patients.

In one of Welty and Robertson's patients the symptoms of increased sugar tolerance overshadowed those of the destructive adrenal lesion and made differential diagnosis very difficult. They believe that with the symptoms of hypoglycemia, Addison's disease should always be considered in the differential diagnosis. Hyperinsulinism and Simmonds' disease may be difficult to rule out. In hyperinsulinism, pigmentation and blood pressure changes are absent and the glucose tolerance curves differ. In Addison's disease the curve is relatively flat; it does not decrease rapidly; and shock is rare without complications. Simmonds' disease is rare, the glucose tolerance curve may simulate that of Addison's disease, but clinical features help in differentiation.

The changes in blood electrolytes in Addison's disease are most interesting. The work of Loeb and his associates[43a,44] and of Harrop and his co-workers[30,31] is well known and will be summarized only briefly here. Loeb noted that the symptoms of Addisonian crisis, nausea and vomiting, increased pulse rate with falling blood pressure, severe pros-

tration, weakness, dehydration and shock resembled the picture seen with depletion of inorganic base in diabetic acidosis, cholera, diarrheas of infancy, and high intestinal obstruction. He studied, in detail, the blood electrolytes both in adrenalectomized animals and in patients with Addison's disease, and found decreases in total base entirely at the expense of sodium. There was an increase in the hematocrit readings indicating a decrease in water content of the blood, a decrease in bicarbonate or chloride content of the serum, or both. When changes developed rapidly, blood urea increased before oliguria and anuria developed. These changes accompanied an actual increased loss of sodium through the kidneys and enough sodium was excreted to indicate a loss from interstitial fluid as well as from the blood. Urinary chlorides and volume increased as well as urinary sodium. Chloride changes paralleled those of sodium but were not as great.

These findings have been confirmed by Harrop and his group.[30] In permitting adrenalectomized dogs, maintained on cortical extract, to go into crisis they demonstrated a shock-like syndrome produced by loss of body fluids. The findings, in sequence, were progressive hemoconcentration, loss of weight, anorexia, lowered body temperature, lowered oxygen consumption, muscular weakness, vomiting, diarrhea, with ultimate failure of the circulation manifested in diminished blood flow and reduced blood pressure. Blood urea rose and plasma chlorides and plasma total base fell at the expense of sodium. Blood magnesium and potassium rose. Harrop, however, has shown no appreciable loss in the water content of liver and muscle tissue.

A number of explanations for these changes have been offered.[44] Were some organic acid to take out fixed base as in diabetic acidosis, ammonia production would increase. It has been reported as reduced. If sodium loss were due to water loss, one could not account for the fact that sodium loss exceeds water loss. Likewise, with primary water loss, blood sodium would rise rather than fall. The most likely explanation is the regulation of sodium metabolism by the cortex. The high blood potassium has also led to the view that disturbed metabolism of this element is the basic fault.[84] Zwemer and Truszkowski found that maintenance of high blood potassium levels in normal animals produced symptoms similar to those of adrenal insufficiency. They believe that regulation of potassium metabolism is an important function of the adrenal cortex and that symptoms of crisis may be considered secondary to the rise in potassium. At any rate, the above findings[31b] make unnecessary the assumption that the suprarenal cortex or its hormones has a detoxifying action on some product of metabolism. They show that the process involved is essentially shock associated with progressive loss of plasma volume, lowered general metabolism and blood flow as well as later lowering of body temperature and blood pressure. Hemoconcentration is thus said to produce circulatory collapse and explains loss of weight, lowered body temperature, anorexia, diarrhea, and vomiting. It is of interest that, in pituitary basophilism with adrenal cortical hyperplasia, the electrolyte pattern has shown, in most respects, diametrically opposite findings.[46]

It must be recalled, as will be stated below under "Diagnosis" that reduced blood sodium does not necessarily indicate the presence of

Addison's disease, for a number of other conditions will also produce this change.

At first there was considerable difference of opinion as to the mechanism of the hemoconcentration and the nature of the shock picture. Loeb's findings, that fluids are lost from the body, have already been stated. These have been confirmed many times. He stated further[43b] that in certain instances loss of base and water does not appear great enough to produce the profound peripheral circulatory collapse encountered, and suggested that there may be some regulatory control of the vascular bed directly. Swingle and his associates[71,72] were unable to account for the dehydration and the associated changes in experimental adrenal insufficiency on the amount of fluid lost as urine, suggesting a mechanism similar to histamine shock. Collapse and hemoconcentration have been observed[70] in adrenalectomized dogs, following withdrawal of cortin, without loss of sodium, chloride, or water in the urine, and the symptoms have been relieved with cortin alone; still a reduction in the amount of interstitial fluid has been shown.[28] Swingle and his associates felt that the relief they obtained resulted from mobilization of intracellular fluids and electrolytes. Harrop offers a similar suggestion and states that blood concentration in adrenal insufficiency may be due to 3 factors: 1, the movement of extracellular fluid to tissue cells; 2, drainage of plasma water into extracellular fluid; and 3, an increased urinary output. He feels the first is the most important.

Most interesting, in the light of the above findings, is a recent report by Hartman and his associates.[34] They have demonstrated that the factor which causes retention of sodium in normal animals can be separated from the vital factor, cortin, by repeated extractions with ethyl ether. The cortin content of the extract was assayed on adrenalectomized cats; the presence of the sodium factor by the effect on sodium retention in normal dogs. They have made many preparations with a high cortin content but no sodium-retaining power. Adrenalectomized cats have been maintained in good condition with no significant weight changes with plasma sodium levels characteristic of untreated animals in an advanced stage of insufficiency. Reduction of cortin to the point of insufficiency produced little change in the plasma sodium while addition of the sodium factor caused a rise of plasma sodium to normal levels. The inability of the sodium factor to maintain both adrenalectomized cats and dogs was demonstrated.

They interpret the evidence as indicating a separate adrenal hormone responsible for sodium retention. In the absence of this hormone cortin maintains the adrenalectomized animal in spite of the diminished plasma sodium. These findings bring up many interesting problems, and if confirmed, will change considerably present views of cortical hormone function.

The elevation in blood urea suggests that renal function may be impaired in Addison's disease, particularly since removal of the glands from animals has also resulted in reduction in P.S.P. excretion.[49] Urea clearance is also diminished,[43b,66] and since these changes occur after omission of cortical extract in adrenalectomized animals, it is considered cortical in origin. Salt therapy, as well as cortical extract, tends to bring these three changes back to normal. Loeb lists the following as evidences of alteration in renal function from lack of cortical hormone:

1, elevation of blood urea, creatinine, phosphates, and sulphates; 2, diminished urea clearance; 3, reduced excretion of P.S.P.; and, 4, increased sodium excretion. To this may be added potassium retention, but whether this represents a manifestation of disturbed renal function or a more general disturbance of potassium exchange is not known.

More recently Willson and Sunderman[82] have shown in a patient with Addison's disease on restricted water intake a retention of sodium and chloride and a reduced urea clearance during the period of oliguria. Simple restriction of water resulted in symptoms of severe adrenal insufficiency. They believe these changes must be the result of the failure of the adrenals alone, for no coincidental renal disease was found. Swingle and his associates[71] found in adrenalectomized dogs an inverse relation of the blood urea nitrogen to the blood pressure. Elevation of urea nitrogen occurred simultaneously with the fall in arterial pressure and did not precede it. They think that the azotemia is probably extrarenal in origin and may have no necessary relation to the kidney. It is also possible that impaired circulation through the kidney may account for reduction in P.S.P. excretion and reduced urea clearance.

The exact mechanism of many of the findings of Addison's disease is not known. The relationships of the changes in blood volume, dehydration, and so forth, to hypotension, gastro-intestinal disturbances, weakness, and other findings has already been given. Loeb has pointed out that oxygen consumption is not affected until 4 days after the withdrawal of maintenance cortical extract in animals and suggests it may be secondary to the dehydration. The mechanism of neurologic findings, such as confusion, disorientation, aphasia, reflex changes, and convulsions of acute insufficiency is not understood. Neurologic changes have been ascribed to hypoglycemia and at times result from this change. However, they do occur in the absence of hypoglycemia and may result[43b] from decreased cerebral circulation as a part of the more general picture of dehydration and shock.

Infection may precipitate crisis and appears to affect cortical function as it does the islet function in diabetes.

There is a large literature upon the possible effects of cortical function on immune reactions. This will not be reviewed here.

There is little definite information concerning the genesis of the pigmentary changes in Addison's disease. It is not always present and is reported both as lessening with treatment with salt and cortical extract, and as being unchanged.[31a,81c] Wilkinson's patients showed a marked disappearance of pigmentation from the mucous membranes, but not from the skin. Harrop found that treatment may slowly lessen the pigmentation of the skin, as did Wilkinson. He ascribed the change to a cessation of excessive deposits and mechanical wearing away of the outer layer where pigment is deposited. Some feel that the rather sudden lessening of pigmentation in several days following recovery from crisis is due to rehydration and its effects on the appearance of the skin rather than to actual change in pigmentation itself. This is further suggested by a rapid return of the color if the patient again goes into crisis.

The pigmentary changes may be related in some way to vitamin C metabolism. This brings up the possible relation of vitamin C to cortical function. It is well known that the middle zone of the cortex contains

large quantities of vitamin C and it has even been suggested that the adrenal gland may synthesize this vitamin. Flowers and Young[21] feel that, with a greater concentration of vitamin C in the adrenal cortex than in any other tissue except, perhaps, the pituitary, one can hardly assume it is just stored there, because of the small size of the area and the great daily excretion. They believe it more logical that vitamin C has an integral part in the function of the cortex. Vitamin C is a reducing agent. They state further that perhaps the pigmentation is explainable as a result of vitamin C deficiency associated with the skin oxydase reaction, for melanin is composed of a benzene ring base and can be produced by oxidation of tyrosine. Reduction of tyrosine leads to adrenalin. Since little adrenalin is said to circulate in the blood of these patients it seems plausible to them that some of the ingested tyrosine has been converted into melanin because the body can no longer convert it into adrenalin. These considerations are purely theoretical. However, low blood cevitamic acid levels are found in patients with Addison's disease whether or not it is due to failure of the adrenal glands to participate in vitamin C metabolism. Patients are said[21] to grow worse when vitamin C is withdrawn from the diet.

Other observations lend some weight to the participation either of vitamin C in cortical function or of cortical function in vitamin C metabolism. A deficient mechanism for storage of vitamin C has been demonstrated in adrenal insufficiency.[24] Wilkinson[81a] found that the degree of subnutrition paralleled the severity of the disease, which other patients in a low state of health did not show. He discards low intestinal absorption as a factor, for gastro-intestinal symptoms were under control in his patients who also responded to oral cevitamic acid. Increased need or destruction of the vitamin is more likely in a febrile disease than in a disease with subnormal temperature and metabolism. He, too, considers, from the richness of the gland in vitamin C that it may have a function in the oxidation-reduction potentials in the adrenals and would thus serve to stabilize adrenalin and cortin. Vars and Pfiffner,[75] from work in dogs, state that if the adrenals play any rôle in the metabolism of vitamin C, it is conferred by the adrenal cortical hormone. Finally, Wilkinson, as did Flowers and Young, suggested that cevitamic acid may be concerned with the regulation of pigmentation of the skin. It is known to inhibit pigment formation *in vitro*, and Hoff[37] has reported alleviation of pathologic pigmentation in scurvy and Addison's disease by its use. Others have reported relief of marked pigmentation by cevitamic acid therapy.[58]

The possible relationships of other vitamins, particularly the B group to the adrenal gland has been discussed by Hartman.[32]

Cardiac mechanismal disturbances have been noted by electrocardiography in Addison's disease.[18]

Diagnosis. Diagnosis in Addison's disease may be simple when the cardinal symptoms are present. Pigmentation is almost essential to definite diagnosis by bedside methods alone, for other features of the disease are common in other conditions. The pigmentation varies, but Snell[62b] has recounted certain characteristics which are helpful in diagnosis. It is most pronounced on exposed surfaces, is diffuse, and is accentuated at pressure points and scars. Freckles, black and minute, are often noted on the neck and shoulders. The genitals, anus, axillæ,

nipples, and lips show accentuation of pigmentation. The oral mucous membranes are involved. The dorsum of the hand may be darker than the palm with a well defined line of demarcation. Biopsy shows only increased melanin. In less clear cut and atypical cases, diagnosis may be difficult and may require the use of special procedures.

The special procedures of value used in diagnosis may be divided into 2 groups: 1, attempts to precipitate crisis, or the electrolytic changes accompanying crisis; and, 2, attempts to relieve symptoms or changes in blood chemistry by the use of cortical extract. The first group consists of several well recognized procedures. The demonstration of sodium disturbances in Addison's disease quickly led to the introduction of the salt deprivation test, or salt-free diet, in diagnosis, particularly since blood sodium levels may be low in conditions other than Addison's disease and Addison's disease may occur with normal blood sodium levels. Withdrawal of salt may precipitate crisis, and in doubtful cases is of definite value.[31a] Signs of relapse may occur as early as the second day, but as a rule 4 to 5 days are necessary. The blood sodium may drop rapidly as compared to that of patients with other diseases, regardless of the initial values.[44] Patients with normal cortical function show no appreciable changes in blood electrolytes. The test is not infallible, and Johnson[38] has described a patient, later autopsied and found to have atrophy of the adrenal cortex, who, on a diet containing only 1.5 gm. daily of sodium chloride for 21 days, failed to show any change in plasma chlorides and urea nitrogen. When the test is used, patients must be closely watched for symptoms of crisis, and means of combating crisis, including intravenous salt and glucose solution and cortical extract, must be on hand for emergency treatment. Patients have died suddenly during or after the test.[42]

The dangers and obvious restrictions of the salt deprivation test have led to the development of other procedures in diagnosis, involving control of the potassium intake. In 1931 Hastings and Compere[35] associated increased blood potassium with adrenal insufficiency. Loeb found similar changes in the blood potassium. Zwemer and Truszkowski[84] produced death in a few hours by administration of potassium to the adrenalectomized cat. Then, in 1937, Nilson[52] precipitated crises in adrenalectomized dogs maintained on low potassium, low sodium diets by feeding potassium. This led to the application of methods of potassium control to diagnosis in man.

Cutler, Power, and Wilder[17a,b] undertook to devise a standard test of the rate of excretion of sodium and chloride as a diagnostic index. They formulated a 3-day examination. On the day preceding the first day of the test, the patients received a general diet with no added salt. Then the test was begun with a diet including 0.95 gm. Cl ion, 0.59 gm. Na ion and 4.1 gm. of potassium. Fluid intake was controlled, and measured quantities of potassium given on the first and second days. Blood and urine samples were collected at stated intervals. It was found that the concentration of chloride in the urine of the third morning was diagnostically more significant than the volume of urine, the potassium concentration of the urine and the total excretion of the various ions. If the concentration of chloride in this specimen exceeds 225 mg. %, Addison's disease is strongly suggested; if less than 125, it is unlikely. The test has been found useful by others.[45] It exposes the patient with

Addison's disease to less risk of collapse than further salt restriction, but is not without danger. Cortical extract and intravenous glucose and saline solution must be kept on hand for emergency purposes and should be administered at the end of the test if Addison's disease is suspected. Further study is necessary to evaluate this test both as to its usefulness and its specificity, for Greene and Levine[26] have obtained altered potassium tolerance curves in a variety of conditions. The only chemical determination necessary with the test is the relatively simple chloride determination.

Tests involving administration of cortical extract remove the danger of precipitation of crisis, but, when based on objective data, involve extensive chemical determinations. One cannot depend upon the presence or absence of subjective improvement following the administration of cortical extract, as Kline[40] has pointed out. Kline's patient, who had a negative salt restriction test, improved markedly on injections of distilled water. However, objective changes produced by cortin may be used in diagnosis. Thorn, Garbutt, Hitchcock, and Hartman[74a] have shown that daily cortin injections equivalent to the daily requirement of a severe case of Addison's disease produce only slight effects on the electrolytic balance of normal human subjects, although it is possible[74b] to obtain measurable effects if sufficiently large amounts of hormone are used. With doses used in treatment, a positive effect of cortin on sodium and chloride balance of a patient suspected of Addison's disease makes the diagnosis more likely. In females, variations in electrolytes may occur at or near the catamenia, and must be taken into consideration.

Changes in dextrose tolerance and low fasting blood sugar often occur in Addison's disease, as does increased sensitivity to insulin. However, these changes occur in other conditions. Demonstration of calcification of the adrenals by Roentgen ray examination is very helpful if present, and in Snell's hands has been pathognomonic.

Treatment. Thorn[73] has recently reviewed adrenal cortical hormone therapy in these columns and little in addition need be said here. The reader is referred to his excellent review, which contains, as well, a discussion of sodium chloride therapy, and the use of the newer synthetic hormone preparation, desoxycorticosterone acetate.

It is only in the past decade that satisfactory cortical extracts have been available and the relationship of salt metabolism to cortical function studied in detail. Hence the two strongholds of treatment, hormone and salt, are relatively recent in their development. Cortical extracts have been used as far back as 1896, when Osler reported good results in one patient with an oral glycerine extract,[53] but their use was not satisfactory until about 1930. Also salt therapy was known to benefit adrenalectomized animals as early as 1925–1927[8,48,68] but it remained for Loeb to demonstrate its effectiveness in therapy in 1933. In the meantime, changes in potassium concentration in the blood and urine had been demonstrated,[35,43a] and, following Nilson's demonstration[52] in 1937 that crises could be precipitated in adrenalectomized animals by its administration, the low potassium diet has been added to the therapeutic armamentarium.

There are several reports outlining the details of the handling of patients with Addison's disease, and for detailed management, the reader

is referred to the original reports.[57,65,81b,c] Treatment may be resolved into two phases, treatment of the chronic or latent stage, and treatment of the crisis. Both involve the use of general measures, such as bed rest until stabilization of the blood chemistry is reached, warmth, and dietary measures, including high carbohydrate, adequate vitamin C content, and at times control of the potassium content. Directions for the preparation of low potassium diets are now available.[76] Treatment of underlying disease, if present, and avoidance of factors which may precipitate crisis, such as infection, overexertion, and exposure to cold are important. More specific measures, important in both stages of the disease, include salt and hormone therapy, and in crisis the treatment of dehydration.

Details of the handling of the patient in crisis have been outlined in the excellent paper by Rynearson.[57] During the early period of treatment the patient needs quiet and complete rest, large doses of cortical extract, up to 50 cc. daily, given in divided doses, parenteral fluids containing glucose, sodium, chloride and little or no potassium. Fluids are given by mouth when they can be taken and these are also fortified with sodium salts. Fluids and cortical extract are continued in large doses until symptoms and the blood chemistry, especially urea and chlorides, indicate a return to normal. This may be 2 to 3 days or longer. With a response the symptoms and signs disappear, metabolism, if depressed, rises, and blood urea and other constituents return to normal. Appetite returns and the weight begins to rise. Cortical extract is then reduced until a maintenance level is reached. This usually ranges from 1 to 5 cc.[65] and at times it may be stopped altogether with a high sodium diet.

In the chronic stage of the disease there is a wide variation in the measures necessary to keep the patient controlled. Some, apparently with considerable functioning cortical tissue may require only salt therapy. As high as 2 to 3 gm. 6 times daily may be given in milk or capsules. Such doses are often emetic and must be reduced. At times a mixture of sodium salts, sodium chloride, sodium bicarbonate, and sodium citrate, may be tolerated better. Chloride must always be given for chloride deficiency exists.

If added sodium salts alone are insufficient to support the patient, reduction of potassium intake may keep the patient symptom-free. In patients treated for crisis it may be possible later to eliminate completely cortical extract or reduce the dosage by this means. The great value of salt therapy in the chronic stage lies in its ability to lower hormone requirements and reduce the cost of treatment.

With complications, such as the common cold, or in the presence of pulmonary tuberculosis, cortical extract may be necessary, if not used before, or the dosage may be increased. Many patients without obvious complications require cortical extract for control. A number of factors, such as infection, the type of adrenal lesion, the "irreversible state," and extra-adrenal disease, may modify the response to cortical extract.

Modern treatment has added much to the usefulness of the patient, but frequently little to his life expectancy.[25] It has definitely prolonged life in a limited group. Patients feel well. They survive hot weather, infections and operations, and can lead an active life.

All patients do not react favorably to treatment[9] even when the blood

chemistry returns to normal.[57] This may be related in some way to the demonstration of Hartman and his associates that the principal essential to life may be separated from the fraction controlling blood chemistry. At times patients return to crisis and large doses of extract fail to produce remission, the so-called "irreversible condition."[33]

Complications of an endocrine nature from injections of cortical extract are rare. Edwards, Shimkin, and Shaver[19] found hypertrophy of the breast in a man due to injections of cortical extract, and were unable to find a similar case in the literature. The gynecomastia subsided with omission of the extract and recurred when the extract was resumed.

Many attempts have been made, both in animals and in man to treat Addison's disease with adrenal grafts.[6,23,36,83] Results, when suggestive of improvement, have all been questionable in patients.

Snell[62a] has pointed out that the number of patients with Addison's disease and tuberculosis who will live long enough for tuberculosis elsewhere in the body to become a menace is increasing, due to present methods of treatment. He believes that the old view, that tuberculosis has no effect on the duration of life in Addison's disease, may have to be revised and treatment for tuberculosis, both medical and surgical, will form an essential part of the treatment of increasing numbers of these patients.

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PEDIATRICS.

UNDER THE CHARGE OF

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DISEASES OF THE KIDNEYS IN INFANCY AND CHILDHOOD.

Normally at birth the urologic system has been fully developed for some time, although it does not actually assume its functional responsibilities until after the connection with the maternal circulation has been lost. Congenital anomalies of the kidney occur and references to these are frequent in the literature. It is to be noted that the effects of these abnormalities are not always present in the neonatal period

nor even during the first year or two of life. Lazarus[19] stated that polycystic disease of the kidney is characterized by the formation of cysts within the renal parenchyma due to congenital occlusion of portions of the renal tubular system. He pointed out that in spite of the fact that this disease is congenital, symptoms rarely appear before the fourth decade with the greatest incidence occurring between the ages of 50 and 60, with both sexes equally affected.

Steinberg[31] reported a case of a congenital cyst of the kidney found in a newborn infant. He commented that the old idea that congenital and acquired cysts of the kidney are separate entities has been dispelled since the time of Küster, who was the first to believe that these cysts are present during fetal life. If the child went throughout life with this anomaly, it was probably one that had not progressed very far during the child's intrauterine life. However, if the condition had progressed to any extent, the child died during its fetal existence. The case that Steinberg reported was one in which hydronephrosis was found at birth with polycystic formation in the kidney.

Karsner's[18] reported case of congenital nephritis is of interest not only because of its rarity, but because of its suggestion along the line of etiology of nephritis. While infection and the presence in the body of some fairly well-defined irritant are generally conceded as causes of nephritis, the occurrence of this disease in the newborn child of an apparently healthy woman leads one to think that this finely constructed gland may be susceptible to the irritation of many substances of which little is known.

According to Fullerton,[15] Henry Morris classified cysts of the kidneys as follows: 1, the small and numerous cysts which occur in granular kidneys and which are of pathologic rather than of clinical importance; 2, dermoid cysts; 3, simple cysts; 4, conglomerate cysts, polycystic disease or cystic metamorphosis of the kidney; 5, hydatid cysts; 6, paranephric cysts or cysts which are external to the capsule and formed in the circumrenal fatty tissue, but which are intimately adherent to the kidney and sometimes communicate with the renal cavity. The specimen reported in this presentation was apparently one of the fourth group. These are nearly always bilateral and the entire kidney structure is affected, both medullary and cortical portions alike. Because it was unilateral the case reported is rather unusual. Banssillon and Guichard[4] discussed theories concerning the pathogenesis of polycystic disease of the kidney under the headings of the hematologic theory, the theory of congenital weakness, that of cicatricial sclerosis and that of productive inflammatory hyperplasia. These writers are inclined to the theory of inflammatory origin because of the numerous inflammatory inclusions in the intercystic walls. These lymphoplasmocystic layers, which are frequently intraglomerular and sometimes perivascular, point to an infectious process of perhaps hematogenic origin.

Masmonteil and Schreiber[21] reported a case of a child who had a bilateral congenital hydronephrosis. The interesting point in this case was the fact that the child survived. At the age of 3 years the first operation was performed. At this time the left kidney was found to be entirely cystic and was removed. Two years later there appeared recurrent attacks of pain and anuria followed by polyuria. The attacks became more severe and more frequent and the patient was admitted

to the hospital after he had had retention for 3 days. At the second operation, the dilated renal pelvis was exposed and opened. It contained a dark, cloudy urine. A Nélaton catheter was inserted and the wound was partially closed. The child was relieved at once but no urine passed into the bladder. It was shown that there was an obstruction at the vesical orifice of the ureter. At a third operation, a transplantation of the right ureter was performed and after 10 days urinary drainage was established through the right ureter. The restoration of function in the sole remaining kidney was a very unusual result for this commonly fatal condition.

Schulz[28] stated that Herxheimer noted the presence of hyaline glomeruli in the kidneys of 80% of newborn infants and nurslings examined by him. He ascribed such glomeruli to maldevelopment and regression of completely developed glomeruli. The author, working in Herxheimer's laboratory, made a microscopic study of the kidneys of 52 fetuses and very young infants. His material consisted of 11 fetuses less than 48 cm. long, 15 newborn infants, 8 nurslings up to 1 month of age and 18 nurslings over 1 month. Hyaline glomeruli were seen in 90.3%. The 5 cases in which such glomeruli were not found were fetuses less than 35 cm. long. The most common localization of hyaline glomeruli was in the middle and deep zones of the cortex. As a rule, they were present in otherwise normal kidneys, although they were associated occasionally with focal subacute inflammatory lesions in the kidneys of the older infants. Although focal inflammation may lead at times to hyalinization of isolated glomeruli, the occurrence of the process in the kidneys of fetuses and in kidneys that reveal no degenerative or inflammatory reactions lead the writer to conclude that hyalinization of isolated glomeruli of infants is usually the result of maldevelopment.

For Dietl[12] albuminuria in childhood is either a sign of organic disease or merely a functional disturbance. The underlying organic disease may be external, such as an infection of the efferent urinary pathways, cystitis or pyelocystitis. On the other hand, it may be strictly renal, such as an inflammatory process in the glomerular apparatus which is called a nephritis, or a degenerative process in the tubular apparatus which he termed a nephrosis. Pure forms are rare as there are nephritides with nephrotic features and *vice versa*. Dietl called attention also to functional albuminuria in the child. This is usually called orthostatic albuminuria because it only occurs in the erect posture. One theory of the cause of this phenomenon is that a change from the horizontal to the erect posture causes in these vasolabile individuals a whole syndrome of vasomotor weakness, or a circulatory reaction, of which the albuminuria is only a rather unimportant partial symptom. The direct cause of it may be a relative ischemia of the kidneys, which goes with the rest of the changes such as accumulation of the blood in the abdomen, relative ischemia of the heart and brain and the like.

Nowak[24] examined 4500 boys between the ages of 14 and 17. Orthostatic albuminuria with lordosis was present in 248 (5.5%). Orthostatic albuminuria without lordosis was present in 276 (6.1%). Chronic kidney trouble was present in 36 (0.8%). Classifying the cases with lordosis, he found that there was some relationship between the degree of lordosis and the severity of the symptoms. The absence of lordosis in so many cases led him to seek other causes and he redivided the boys

into another three groups: those with general muscular flaccidity and postural defects, those with special susceptibility to catarrhal infections with adenopathy and large tonsils and a miscellaneous group with neuropathic tendencies, dental caries and chronic disease of the middle ear. In the first group there were 142; in the second, 77; in the third, 29. He concluded that lordosis is probably a definite cause of orthostatic albuminuria, but that the condition can be brought on by many other constitutional abnormalities that lead to changed circulation in the kidneys.

From the standpoint of malignancy, Mixter[23] reported that during 21 years in 22,000 admissions to the surgical wards of the Children's Hospital in Boston there were recorded 41 instances of renal neoplasm. It was found that malignant growths occurred in childhood at any age irrespective of sex. Most of them were seen in the first 5 years of life. Symptoms were usually absent at first in childhood but as the tumor grew the child became irritable and gave evidence of abdominal discomfort, although pain was rare. There was usually secondary anemia. In the terminal stage, there were dilatation of the superficial abdominal veins and rapid wasting. Metastases usually occurred by way of the blood stream and involved the lungs, liver and occasionally the opposite kidney.

Campbell[9] estimated that about one-half of all children suffer from some urologic disturbance at some time before puberty. Many of these disturbances are minor and very frequently are not recognized. On the other hand, many important conditions are overlooked through failure to make simple routine examination of the urine of all sick children. The most common symptoms met with in children having urologic lesions are pyuria, disturbances of urination and nephritis. Obstruction is found to be the most frequent predisposing cause of infection. Congenital stricture is the most common abnormality of the upper part of the urinary tract, but the obstruction may occur at any point from the preputial orifice to the renal calyx. Aberrant renal vessels are a frequent cause of obstruction and about one-fourth of all kidneys have some anomalous vessels. The embryonal adenomyosarcoma of Wilms is the most common abdominal tumor found in children, but hydronephrosis is the most common palpable renal tumor in children.

Anderson[3] called attention to the fact that deposition of calcium in the kidneys occurs frequently in infancy and childhood in association with a variety of conditions. Occasional small deposits seem to have no significance. He reported 20 cases of marked renal calcification. The calcium was most frequently limited to the cortical region and involved tubules. In 4 patients who had received parathyroid extract and calcium salts, the deposits were also found in small blood-vessels. Evidence of renal damage was almost invariably found both clinically and at autopsy. Capon[10] also reported a case showing renal calcification but his case showed a renal rickets. Roentgen examination of the kidneys showed calcareous deposits in the calices of both kidneys, the pelves and both ureters.

In a study of urinary lithiasis in infants and children and in a review of the literature Ercole[13] found a lower incidence in his series; of 60 cases reported, 8% were in children. There was no predilection of sex.

Most of the calculi were formed of uric acid crystals or urates, calcium oxalate or triple phosphates. Calcium oxalate and ammonia urates formed the nuclei in the majority of the cases. These two substances were four times as frequent as uric acid. The presence of triple phosphates indicated the changes due to infection as a result of the calculi. The majority of the calculi (70%) were found in the bladder.

Aldrich[1] has advocated a classification of nephritis in seven groups, based on clinical signs rather than on anatomic involvement. The first group was called acute postinfectious hemorrhagic nephritis and was characterized by an antecedent or concomitant acute febrile infection, hematuria and either a benign course or death during the acute illness. Second, chronic non-specific nephritis, was characterized by edema, hematuria, hypertension, increase of non-protein nitrogen in the blood and a chronic course or death. The third group, nephrosis, was characterized by marked edema, absence of hematuria at all times, normal blood pressure, normal blood non-protein nitrogen and marked albuminuria. The fourth group, subacute bacterial endocarditis with nephritis, showed edema, signs of subacute bacterial endocarditis with albumin, casts, red and white blood cells in the urine. The fifth group, syphilis with nephritis, showed the clinical picture of chronic non-specific nephritis, or Group II, plus the evidence of an active syphilis. The sixth group, tuberculosis with nephritis, also gave the clinical picture of Group II plus the evidence of miliary tuberculosis. The seventh group, renal infantilism, also showed the clinical picture of chronic non-specific nephritis but in addition the physical evidence of infantilism.

Bell[5] suggested that subclinical glomerulitis differed from clinical glomerulonephritis only in intensity. A large number of infectious and toxic processes are concerned in the etiology of the disease. The glomerular capillaries are injured by various toxic substances. Sensitization to bacterial or to other protein may play an important part; but it is not necessary to assume that sensitization is essential in the development of the lesion. From a study of a large series of cases it was concluded that a definite preponderance of endothelial over epithelial cells represented a glomerulitis. The glomerulitis seemed to be due chiefly to endothelial proliferation, but the lodgment of mononuclear leukocytes in the capillaries also played a part of some importance. There was no anatomic base for a diagnosis of focal glomerulonephritis except in instances of transitory glomerular bleeding not associated with symptoms of nephritis, and in cases of bacterial endocarditis.

Snoke[30] was convinced that glomerular nephritis in childhood was a much more serious disease than is generally believed. After the initial attack the disease may persist for many years. The existence and persistence of latent glomerular nephritis often escapes detection when quantitative examination of properly concentrated urine is not made. It is to be remembered that glomerular nephritis commonly and nearly always enters a latent stage after the initial stage. It is possible for the initial stage to be overlooked when gross hematuria or fulminating symptoms are absent. Latent glomerular nephritis may terminate in healing or may pass on to the degenerative stage or to the terminal stage. The duration is exceedingly variable, and the later stages may not appear until adult life. The prognosis for the successive stages of

glomerular nephritis, active, latent, degenerative and terminal, are successively worse in the order named and the last named is uniformly fatal. The age of the patient at the onset of the disease did not seem to have any influence on the prognosis. Hypertension and increased amounts of blood urea have similar significance and tended to parallel each other. In the initial stage, there is no relation to prognosis of hypertension and increased blood urea concentration, but when they appeared in the later stages they supplied the first indications that the patients were entering the terminal stage of renal insufficiency. The value for blood urea did not become abnormally high as a general rule until one-half of the renal tissue failed to function.

According to Bierman,[6] the diagnosis of acute glomerular nephritis is based on the sudden appearance of red blood cells, casts and albumin in the urine accompanied by some edema and rise in blood pressure either during or following some acute infection such as tonsillitis or scarlet fever. In a majority of cases the symptoms gradually subsided, the urine cleared up in the course of a few weeks and the child seemed well in every way. He described the Addis sediment count or concentration method (a 12-hour specimen of urine is rendered acid and concentrated simply by restricting the fluid intake for the day preceding the test; after timed centrifugalization the sediment is transferred to a blood-counting chamber and the computations made on a 12-hour basis). Four stages of glomerular nephritis have been established through the studies of Addis. The initial stage follows an acute infection which may have been definite or so mild as to have escaped notice. In its more severe form it is characterized by gross hematuria imparting a mahogany brown color to the urine, edema, vomiting, headache, some elevation of blood pressure and occasional severe prostration and convulsions. This initial stage may go on to healing or progress to more advanced stages. The second or latent stage may be asymptomatic but may be diagnosed by the continued excretion of red blood cells, casts and albumin which may be so slight as to escape notice. This stage may last a few weeks or several years. The third or degenerative stage is characterized by marked albuminuria with large numbers of casts, epithelial cells and leukocytes, together with a small but noticeable excess of red blood cells. Sometimes a decrease of serum albumin, increased plasma lipoids and general edema may occur. Without the Addis test this stage may be confused with a nephrosis. The fourth or terminal stage is characterized by the appearance of headache, vomiting, retinal changes, hypertension and azotemia together with increased amounts of albumin, blood, epithelial cells, and casts. This stage may last only a few days or many months.

Glanzman[17a] stated that glomerulonephritis is by far the most common form of kidney disease in childhood. He pointed out that it is typified by the picture seen in scarlatina nephritis. Puffiness of the eyelids, especially in the morning, or hematuria or both are early symptoms. There is an increase in body weight due to the latent dropsy. The kidney symptoms are often preceded by a striking yellowish pallor. Oliguria, moderate albuminuria, granular casts, hypertonia and increased residual nitrogen in the blood are characteristic. Even more common than scarlatinal nephritis is a form seen with impetigo or other infectious skin diseases.

Rubin and Rapoport[25a] found three major complications of acute hemorrhagic nephritis in children: renal failure, hypertensive encephalopathy and eclamptic uremia and cardiac failure. These complications may occur alone or together or may follow each other in the same patient. In the renal failure there were encountered anuria; edema; retention of nitrogenous waste products, urea and creatinine; retention of acid waste products as manifested by the elevated phosphate in the blood and an acidosis as evidenced by low blood carbon dioxide combining power; progressive intoxication as the anuria continued and usually only slight elevation of blood pressure. With the hypertensive encephalopathy there were convulsions, coma and aphasia. The cardiac complications were by far the commonest and most serious complications of the disease. These were hypertension, varying degrees of cardiac involvement, simple dilatation without myocardial failure, cardiac dilatation with myocardial failure, generalized edema and a high blood urea concentration.

Rubin and Rapoport[25b] studied 55 cases of acute hemorrhagic nephritis in children. Severe myocardial damage was encountered in 14 of the patients and 12 had signs of frank cardiac decompensation. Hypertensive encephalopathy was found in 5 and uremia in 2. The only 2 deaths in the whole group were due to acute cardiac failure. The clinical evidences of cardiac involvement included dyspnea, tachypnea and cough, cardiac enlargement, muffled heart tones, rapid heart rate, murmurs which were usually mitral systolic, gallop rhythm, enlargement and tenderness of the liver, engorgement of the venous system, pulmonary edema, peripheral edema and electrocardiographic changes. They emphasized the importance of hypertension as a cause of cardiac decompensation as they found hypertension in all cases in which there was cardiac involvement.

Discussing chronic nephritis in childhood, Geldrich[16] advocated the classification of the hematogenic renal diseases of Volhard and Fahr. In the group of monosymptomatic forms there is first nephrosis, the cardinal symptom of which is edema. The next heading is sclerosis, the cardinal symptom of which is hypertonia. The third heading is focal nephritis, the cardinal symptom of which is hematuria. Under the group of polysymptomatic forms there is the heading of diffuse glomerulonephritis, in which are united all the cardinal symptoms of the monosymptomatic group. These are further subdivided into an acute type which is curable and a chronic type which is incurable and progressive.

Bruce[8] gave a simple but adequate classification of nephritis in childhood as acute nephritis, chronic nephritis and nephrosis. Lyttle[20] stated that the two common kidney conditions found in children are acute glomerular nephritis or hemorrhagic Bright's disease and nephrosis or degenerative Bright's disease. Of the latter, he listed as typical clinical findings an insidious onset without preceding infection, edema, albuminuria, oliguria with high specific gravity, low serum protein, high blood cholesterol, low basal metabolic rate, a chronic course and pathologically tubular degeneration.

Waring[33] stated that the symptoms of nephrosis are quite classical and well recognized. Edema is usually the first symptom and is insidious in its approach. The urinary changes include albuminuria which

is marked and constant, and casts at times and at other times none. There is a noticeable absence of the cellular elements, particularly the red cells. Oliguria is marked. Doubly refractile lipoid bodies are sometimes found. The blood changes include lipoidemia with a marked increase of blood lipoids, especially cholesterol. There is usually a reversal of the usual albumin-globulin ratio of 2 to 1 with general low protein content. The anemia may be marked. The basal metabolism rate is often low although there is apparently no change in the secretory activity of the thyroid gland. Fatigability is a natural and constantly present symptom. As opposed to the changes of glomerular nephritis, there is usually a normal non-protein nitrogen, normal blood pressure and absence of hematuria. The functional kidney test may be normal and there is an absence of uremic symptoms.

Westcott and Dennett[34] described nephrosis as a metabolic disease accompanied by changes in the blood lipoids and proteins, and manifested pathologically by degenerative processes. The cause of this condition is not known. Edema is an outstanding feature, but it is not directly of kidney or circulatory origin and is not entirely related in cause or effect to the blood proteins. The authors believed that it was of metabolic origin and that it followed more or less directly the blood lipoids and their metabolism with the resulting change in tissue osmosis due to depleted proteins and increased cholesterol. There is usually an anemia accompanying this condition. This is out of proportion to the loss of kidney function. They felt that the prognosis of primary nephrosis was unfavorable and the same was found to be true of the secondary types that result in chronic nephrosis. The lesion is essentially a lipoidal degeneration with a superimposed infectious element.

Schwarz and Kohn[29] found that there was no constant relationship between the height of the blood-cholesterol level and the basal metabolic rate. There was also no constant relationship between the total serum proteins and the patient's weight. In the same way, the body weight, which was a criterion of the extent of the edema, showed no constant relationship with the blood-cholesterol content. When the serum-protein value was low the cholesterol content was usually high, but even this was not constant. This indicated that an increased blood-cholesterol content did not always take the place of the proteins lost from the blood. In cases with a low serum-protein value it was usually the albumin that was excreted. However, in several cases in which the serum-protein value was low, the authors did not always find the expected reversal of the albumin-globulin ratio. They did not find a constant relationship between the intensity of the edema and the amount of protein lost in the urine. The blood-cholesterol content often remained high after all signs of edema had disappeared.

According to Glanzman,[17b] nephrosis in childhood begins gradually with fatigue, loss of appetite, pallor and slight edema of the eyelids at first. In contrast to acute glomerulonephritis there is rapid development of severe general edema with ascites, hydrothorax and even hydropericardium. The quantity of the urine is slight, with a high specific gravity. The urine contains a great deal of albumin, casts of all kinds, especially lipoid casts and double-refracting lipoid bodies, but no red blood cells. The blood serum and the exudates are clouded because

of the large lipoid content. The blood pressure is not increased and real uremia never develops. The child's body seems filled almost to the bursting point with water and then suddenly there is a loss of the edema. This may remain cleared until a new attack develops following a slight infection such as a coryza or bronchitis. The patient is usually a chronic invalid and may die of some intercurrent infection such as pneumococcic peritonitis.

Farr[14a] made nitrogen balance studies on a group of children with the nephrotic syndrome. He used diets which varied in protein content from 0.5 to 4 gm. per kilo of ideal body weight. The maximum nitrogen retention occurred in 4 patients when the dietary protein intake was about 3.2 gm. per kilo of ideal body weight, and in the fifth patient when the intake was 3.6 gm. per kilo of ideal body weight. Feeding more protein resulted in actually less retention. The protein intakes producing maximal assimilation in these nephrotic children were similar to those found by other observers to be optimal for growth and general condition in normal children. He did not find that in the nephrotic syndrome the loss of protein in the urine was accompanied by compensatory increases in ability to assimilate food protein. It was found that there was no support for the supposition that, in patients with albuminuria, the optimal protein intake could be calculated by adding to the ordinary maintenance diet an amount of protein equal to or proportional to the protein loss in the urine. This group failed to assimilate protein fed above 3.3 gm. per kilo, and this emphasized the point that the physiologically optimum intake of a given food is not necessarily the greatest amount that can be handled by the alimentary tract. Still less was there justification for forcing high protein diets such as those to which are added casein or lactalbumin as this might cause gastro-intestinal rebellion.

Blackman[7] studied the etiology, pathogenesis and nature of lipoid nephrosis. He concluded that there was no evidence that lipoid nephrosis is a metabolic disease. He presented clinical and pathologic data which indicated an etiologic relation between chronic pneumococcic infection and the pathogenesis of some examples of lipoid nephrosis. He believed that it was a particular form of diffuse nephritis and that microscopic hematuria and slight elevation of the blood pressure may occur at times. From his data he believed that the edema of nephrosis cannot be explained by mechanical factors alone, and that there is good evidence that widespread capillary damage is one important factor in the pathogenesis of edema of nephrosis.

Mitchell *et al.*[22] made metabolic studies on 5 nephrotic children. They found that the effects of diuretics and dietary treatment varied greatly in producing temporary changes. No prolonged general improvement, including the disappearance of edema, was accomplished with any procedure. The protein content, including the albumin and globulin of the serum, its non-protein nitrogen content and cholesterol content of the blood were determined from time to time. These values were found to be those characteristic of the nephrotic syndrome. These included a low total protein content, a reversal of the ratio of albumin to globulin, a normal value for serum non-protein nitrogen and a high content of blood cholesterol. The concentration of hemoglobin and the cell counts showed no definite changes. The values for

basal metabolism of all the patients were within normal limits according to the standard of Benedict and Talbot, and with one exception to the standard of Harris and Benedict. According to Dreyer's standard the heat production of all patients except one was low. From the determination of caloric intake and caloric loss, calculations were made for the percentage absorption of energy and the expenditure of energy for growth, digestion and activity. These values agreed with data obtained from normal children and indicated that the energy exchange of a nephrotic patient is normal.

Farr[14b] stated that in the majority of instances the basal metabolic rate of children with nephrosis was reported as low. All of the patients were in hospital when these observations were made and all manifested well-defined evidences of the nephrotic syndrome, as manifested by edema, lowered level of albumin in the plasma with reversal of the albumin-globulin ratio, absence of hypertension, lack of retention of nitrogen and definite albuminuria without hematuria. Throughout the periods of observation they were all given comparable weighed diets and there were no known complicating factors. This study comprised 34 tests made on 8 patients. There was no significant deviation from the expected metabolic rates with one exception. It was interesting to note that in no instance was a consistently low basal metabolic rate obtained, but it seemed to be increased in 1 patient. This patient seemed to have a real nephrosis. In another study this same patient did not show increased tolerance to thyroid, nor was he benefited by its administration.

Schiff[26] stressed the importance of the differential diagnosis between nephritis and nephrosis. He said that if a nephrosis is diagnosed and treated for months as a severe nephritis the treatment probably does more harm than the disease itself. The diagnosis of nephrosis may be made on the presence of edema, with or without ascites, developing suddenly without any premonitory signs, a urine with high specific gravity, an abundance of albumen; no hypertonia. In addition, the eye-ground examination showed a normal fundus, there were a cholesterinemia, a lipoidemia, substances with double refraction in the urine sediment and pronounced acceleration of the sedimentation rate of the erythrocytes. It was more difficult to determine whether the case was one of genuine nephrosis or a case of subchronic glomerulonephritis in the stage of nephrosis. Under such circumstances the history is important as the presence of a previous acute nephritis indicated the diagnosis of glomerulonephritis.

In a study of 45 children with the nephrotic syndrome, Tappan[32] attempted to determine whether prognostic criteria could be found which might serve to differentiate cases within the group as well as the general prognosis of the nephrotic syndrome in children. It was found that the outlook was grave for these patients. The mortality rate was 51.1% and the recovery rate only 17.7%. The occurrence of hematuria, whether gross or of lesser grades, associated later in the disease with rising blood pressure, increasing retention of nitrogen and diminishing renal function was one adverse picture, and the occurrence of a pneumococcic peritonitis was another development of grave import. It was found that the outlook was grave for patients with the nephrotic syndrome. When hematuria develops the prognosis becomes hopeless

and the occurrence of a pneumococcic peritonitis markedly decreased the chances of recovery in the cases without hematuria.

Discussing the treatment of nephrosis, Schultz and Collier[27] pointed out that besides its chronicity one of the most disconcerting characteristics is the tendency to alternate remission and severe exacerbation and the reappearance of the condition after long periods of apparent cure. Although considerable progress has been made in the treatment of the condition, no form of therapy is really consistently successful or gives assured relief for the more troublesome symptoms. Among these are the excessive and sometimes tremendous losses of protein in the urine and the development of anasarca and ascites to a degree seldom met with in pediatrics. The albuminuria cannot be prevented, but can be overtreated to the great harm of the patient when excessive limitation of the protein intake is ordered. It has been found that considerable changes in the protein content of the diet have little or no effect on the daily proteinuria. The edema is a great problem in the care of the nephrotic child. Rest in bed is always absolutely essential. Hydrotherapy only helps to a slight degree. Restriction of salt and restriction of fluid intake is of the greatest importance and is usually most helpful. Among other procedures there are recommended thorough removal of focal infections, especially of the upper respiratory tract. These observers had favorable experience in the few cases in which they could employ it with high administration of alkalis as recommended by Osman.

Aldrich, Stokes, Killingsworth and McGuinness[2] treated 9 patients suffering from typical lipoid nephrosis with edema by administering concentrated human blood serum. In 6 cases the lyophile serum produced complete and immediate diuresis. In 1 patient there was delayed and incomplete diuresis, while in 2 cases no beneficial results were noted. Four patients not only lost their edema but had normal urine within a few weeks of treatment and had remained clinically well up to the time of the report. They believed that the injection of human lyophile serum produced some diuretic effect, but they were not certain that the effects produced were the result of a strictly quantitative osmotic action of the serum. If such were the case, they would hardly expect the diuretic effect to go on for many days until the edema was completely eliminated without replenishment with more concentrated serum protein. They suggested that, in addition to its osmotic action, the serum supplies some substance or substances that set off the patient's own mechanism of diuresis.

A number of references concerning renal dwarfism are met in the literature. Debré, Marie and Jammet[11] called attention to a rather curious disease entity which has been described under such terms as renal dwarfism, renal infantilism, renal rickets or chronic atrophic nephritis of childhood with arrest of growth and osseous deformities. They discussed those aspects of the chronic atrophic nephritis of childhood which appeared to them to be especially noteworthy. They called attention to the dwarfism, the normal intelligence and the fact that the secondary sexual characteristics fail to develop at the time of puberty. They also reported their observations on the phosphorus and calcium metabolism. In renal rickets there is a hyperphosphatemia and a hypocalcemia, but tetany rarely occurs. This has been ascribed

to the acidosis in renal rickets, which prevents tetany by transforming the largest portion of the calcium into the ionized form. The first manifestations of this renal trouble is manifested usually about the sixth to tenth year. Polydipsia and polyuria are usually present much earlier. The pallor and jaundiced color of the children are outstanding.

Other forms of kidney disturbances are met with in children. Pyelitis is of very frequent occurrence. Enuresis is another frequent abnormality of this system. Although it is not always due to a disturbance of the kidney itself, it is a very frequent and difficult problem in childhood.

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PHYSIOLOGY.

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 15, 1939

A Flicker Spectrophotometer. R. H. Peckham and R. H. Hamilton (Departments of Opthalmology and Biochemistry, Temple University). Parallel light from a diffuse source is passed through colorimeter cups and plungers and then through sector diaphragms by means of which known fractions of the light can be occluded. The parallel light is brought to a focus upon the sharp edge of a revolvable semicircular front surface mirror, the beams from the two sides being brought into apposition by means of three other front surface mirrors. An eyepiece

focuses upon the mirror edge and projects an image of the diaphragm smaller than the pupil into the plane of the pupil. The observer sees a circular field divided by a diametral line, as in the ordinary colorimeter, and matches of the two halves can be made either by adjustment of the depth of solution or by adjustment of the sector diaphragms.

With a second eyepiece the mirror edge can be focused upon the slit of a monochromator, so that comparisons can be made with monochromatic light. If the sector diaphragms are used to measure the light absorbed by a colored solution at various wave lengths, absorption curves can be plotted.

When the revolvable mirror is driven with a motor to throw light from each side alternately into the pupil, the "flicker phenomenon" produced allows accurate photometric measurements to be made by elimination of the flicker.

Growth and Differentiation of Connective Tissue as Observed Microscopically in the Living Rabbit. MARY L. STEARNS (Fellow, Department of Anatomy, University of Pennsylvania). The daily progress of connective tissue regeneration was followed microscopically in the living rabbit in a series of transparent chambers inserted in the ear. The actual differentiation of connective tissue fibrils was observed.

The new growth began within a week after operation, when fibroblasts invaded the table migrating inward at an average rate of 0.19 mm. a day. Fibrils appeared 4 or 5 days later at the edge of the table. They were extended from the periphery to the center of the table at a rate of approximately 0.27 mm. a day, and covered the entire table, 6 mm. in diameter, 3 weeks after operation.

The observations indicate that the presence of fibroblasts is essential to the development of connective tissue fibers which occurs in the rabbit's ear chamber. Furthermore, fibroblasts participated actively in the formation of the first network of fibrils. Small masses of the protoplasm of the fibroblasts were seen to project from or to become detached from the surface of the fibroblasts. These cytoplasmic masses became centers for very active fibril formation, and rapidly diminished in size as the fibrils formed.

There was no indication that fibers were formed by a direct transformation of the fibrin net that follows insertion of the window. In fact the presence or absence of fibrin was immaterial to the process. No evidence was found to indicate that fibers were formed as continuations of preëxisting fibers, or through the activity of any cell but the fibroblast.

Tension influenced the rate, amount, and direction of fibrous development.

The Action of Urea Upon Hemoglobin. A Spectrophotometric Study of the Process of a Protein Denaturation.. DAVID L. DRABKIN (Laboratory of Physiological Chemistry, University of Pennsylvania). With the chromoprotein hemoglobin, visual spectrophotometry was employed in following quantitatively the progress of protein denaturation by various means.

Essentially analogous spectroscopic changes were found to occur when

hemoglobin was treated with alkali, urea and acetamide in high molar concentrations (4 to 6 M), or HCl (0.1 M). In the case of the latter reagent, the familiar acid hematin is produced. The reaction takes time. When, during the course of the reaction, enough alkali was added to just dissolve the material precipitated at the iso-electric point as the acidified solution was neutralized, the presence of typical globinoferroporphyrin (reduced, denatured globin hemochromogen) was disclosed upon addition of $Na_2S_2O_4$.

The primary reaction during denaturation may be typified by the following:

Ferrohemoglobin (HbO_2) + NaOH → Globinoferriporphyrin (oxidized, denatured globin hemochromogen).

With a final concentration of hemoglobin of 0.1 mM per liter (1 mole equivalent to 1 mole of iron porphyrin) and a concentration of alkali equal to 0.008 M, the time required for one-half completion of the above reaction was 13 hours for horse HbO_2, contained in a closed 1 cm. cuvette at 20° C. Under similar conditions, the reaction was somewhat more rapid with dog HbO_2. The alkali employed was a mixture of 0.005 M NaOH and 0.003 M NH_4OH. The latter was included to more than compensate for slight ammonia production which occurred in experiments in which both alkali and urea were used.

The rate of denaturation of HbO_2 in the presence of 6 M urea alone, at 20° C., was of the same order of magnitude as with the above 0.008 M concentration of alkali. The rate of reaction was decreased at lower concentrations of urea, and was appreciably increased at a temperature of 38° C. In the presence of 6 M urea and 0.005 M NaOH, both horse and dog HbO_2 were denatured approximately 60 times as rapidly (13 minutes for one-half completion of the hemoglobin to hemochromogen reaction) as with 0.008 M concentration of alkali alone. This observation is of great interest from the standpoint of the effect of urea upon the molecular structure of hemoglobin.

Ketone Formation and Utilization in Normal and Diabetic Cats. W. C. Stadie, F. D. W. Lukens, and J. A. Zapp, Jr. (Department of Research Medicine and the Cox Institute of the University of Pennsylvania). Ketone body formation and utilization respectively were studied in normal 3 to 4 day fasted and diabetic cats. Liver slices and muscle mince-meat were equilibrated for 2 hours at 38° in Warburg vessels, and the contents were then analyzed for beta-oxybutyric and aceto-acetic acid. The mean ketone formation of diabetic liver slices was found to be 1052 ± 220 micro-moles/kilo of cat/hour, (μM/Kg/hr), while the mean for normal fasted cats was 230 ± 45 μM/Kg/hr.

Utilization of ketone bodies by the intact cat was calculated from the liver production minus the urinary excretion during the hour immediately before death. The mean value in 6 diabetic cats was found to be 970 ± 215 μM/Kg/hr. Utilization of ketone bodies by muscle was demonstrated more directly in two ways: (1) A weighed liver slice and weighed portion of muscle mince-meat from the same diabetic cat were equilibrated in a Warburg vessel for 2 hours at 38°. On the assumption that the liver slice produced ketones at the same rate as parallel slices in the absence of muscle, it was found that the diabetic

cat utilized ketones at the rate of 2070 ± 433 μM/Kg/hr. The oxygen uptake of the liver and muscle together agreed with the sum of the O_2 uptakes observed for each separately. (2) Sodium aceto-acetate was added to muscle mince-meat and the utilization determined directly. The mean utilization of ketones by normal fasted and diabetic cats was found by this method to be 550 ± 300 μM/Kg/hr (6 cats).

Finally, the ratio of oxygen uptake to ketone formation in the liver slices of diabetic cats was 2.26 ± 0.50 : 1 and the corresponding R. Q. was 0.39 ± 0.06. These observations are not in accord with the hypothesis that one molecule of ketone is derived from one molecule of fatty acid, but are consistent with the hypothesis that each molecule of the higher fatty acids yields four molecules of ketone.

Anoxia of the Central Nervous System Produced by Temporary Complete Arrest of the Circulation.* LAURENCE M. WEINBERGER, and JOHN H. GIBBON, JR. (Harrison Department of Surgical Research, University of Pennsylvania). Previous methods used to establish the time that the brain can withstand the effects of circulatory arrest have yielded varying results. The pathologic alterations following upon a single period of circulatory arrest sufficient to cause permanent neurologic signs but not enough to cause death have not been precisely determined. In an effort to reinvestigate this subject a new technique was devised.

The experiments were performed on cats. At a preliminary operation, the left fourth and fifth ribs were resected along with the overlying muscles, the lung pushed aside and the pericardium sutured all around to the cut edges of the muscles. Six weeks later the animal is anesthetized with ether. A small incision is made over the previous site and the pericardium entered without opening the pleural cavity. A clamp is passed around the pulmonary artery. The animal is allowed to come out of its anesthesia and the clamp is then abruptly closed. Thus the bloodflow to the entire body is arrested. At periods ranging from 2 to 9 minutes, the clamp is released. Artificial respiration with a mechanical respirator is started shortly before the clamp is removed to ensure the saturation of arterial blood with oxygen from the moment the clamp is released. An intra-arterial injection of adrenalin and saline is made and the heart is massaged until the ventricular contractions are strong and regular. The retina is continuously observed from the moment the clamp is released and the end of the period of cerebral anoxia is taken as the moment the bloodflow reappears in the retinal vessels. Artificial respiration is continued until spontaneous breathing is established.

The severity of the postoperative neurologic signs and symptoms, and the extent of the permanent neurologic damage varied directly as the length of circulatory arrest. Animals subjected to 3 minutes, or less, of circulatory arrest recovered completely. Those subjected to periods between 3 minutes and 25 seconds and 5 minutes and 45 seconds showed permanent changes in behavior. Those subjected to circulatory interruption of approximately 6 to $7\frac{1}{2}$ minutes showed varying degrees of

* Aided by a grant from the Josiah Macy, Jr., Foundation, New York.

dementia, blindness, postural and reflex changes all of which remained throughout the period of survival. It was not possible to resuscitate animals for more than a few hours if the circulation was interrupted for more than 8 minutes.

The animals were sacrificed for pathologic study at varying periods up to 6 weeks. The pathologic studies revealed that gross cortical necrosis and tissue disintegration can occur following periods of circulatory arrest no longer than 3 minutes and 25 seconds. From this period up to 7 minutes and 30 seconds, the intensity and extent of the cortical destruction increase. In the animals surviving periods of circulatory arrest in the neighborhood of $7\frac{1}{2}$ minutes the cortex was entirely destroyed, disintegrated and fragmented. The susceptibility of the various regions of the brain to circulatory arrest in descending order are: motor and visual cortex, other portions of the cerebral cortex, Purkinje cells of the cerebellum, lateral geniculate nucleus, hypothalamic nuclei, thalamic nuclei, caudate nucleus, midbrain, pons, medulla and spinal cord.

Production of Ovarian Cysts and Urinary Calculi in Young Rats With Testosterone Propionate.* HARRY SHAY, J. GERSHON-COHEN, SAMUEL S. FELS, and KARL PASCHKIS (Medical Research Laboratory of the Samuel S. Fels Fund). Starting in the first or second day of life, 1 mg. of testosterone propionate (Oretone) was injected subcutaneously 3 times weekly into female rats. A total dosage of 40 to 180 mg. was administered. In addition to changes in the clitoris, vagina, uterus, estrus cycle and endocrine glands which have already been described, we observed the formation of ovarian cysts and urinary calculi.

Of 17 treated females (15 sacrificed and 2 orchidectomized), 12 showed ovarian cysts. These ranged in size from 7 mm. to 50 mm. (longest diameter) and in weight from 948 to 62,600 mg. (weight of both ovaries). The size of the ovaries was independent of the total dosage. The smallest total dosage after which ovarian cysts were found to date was 40 mg. The other 5 animals showed atrophic ovaries. Cystic degeneration or atrophy was found in litter mates receiving the same total dosage of hormone. In 1 animal, one ovary was converted to a large tumor weighing 27,000 mg. while the other ovary was atrophic (weight 10.4 mg.).

Histologically, the tumors were lutein cysts. Occasionally follicular cysts were seen as well in some sections.

In 21 treated females (sacrificed and died spontaneously), 11 showed urinary calculi, marked hypertrophy of the bladder, with varying degrees of distention and distortion of the ureters, dilation of the kidney pelves, and atrophy of the parenchyma.

In 1 animal, the kidney pelvis of one kidney was completely filled by a cast-like stone. In 1 numerous abscesses of the parenchyma were found. Urinary calculi were present in animals with ovarian atrophy. In several animals hypertrophy of the bladder without stones occurred.

* We are indebted to Dr. Max Gilbert, of Schering Corporation, Bloomfield, N. J., for our supply of Testosterone Propionate (Oretone).

Perhaps these were cases in which the stones had been passed. While the injection of testosterone propionate does disorder follicle maturation, it does not even in large doses always cause complete cessation of estrus.

In 6 controls, there were no abnormalities of the genital or urinary tracts. In 15 treated male rats, receiving similar amounts of testosterone propionate and sacrificed to date, no calculi or bladder hypertrophy were seen.

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